ANNALS of ALLERGY

Published by
The American College of Allergists

Volume 19 November, 1961 Number 11

THE ASTHMAGRAM

Analysis of Asthmagrams of 100 Consecutive Cases of Chronic Asthma

OSCAR SWINEFORD, JR., M.D., W. P. COLEMAN, M.D.,
H. R. PEARSALL, M.D., and J. C. CURRY, M.D.
Charlottesville, Virginia

ASTHMA is a common but complex human affliction. No other syndrome can be precipitated by as many diverse causes. Successful therapy depends on the recognition of these causes, which are usually multiple in the chronic asthmatic. Good results have been reported in less than 50 per cent of cases of chronic asthma.[1] It is reasonable to assume that a comprehensive diagnostic program, designed to recognize all possible causes, could improve these depressing results.

The dearth of practical instructions for conducting such diagnostic studies[2,3] is surprising. Equally surprising is the absence of analyses of etiologic data obtained by detailed studies of large numbers of cases of chronic asthma. It was with these things in mind that this detailed analysis of the etiological factors in 100 consecutive cases of chronic asthma was undertaken. In this study considerable emphasis was given to the use of the Asthmagram.[3] The Asthmagram is a clinical device which simplifies the classification of etiologic data obtained from asthma patients by history, physical, x-ray and laboratory examinations and by skin tests. Once the recognizable causes of asthma have been classified, the Asthmagram provides an orderly approach to the management of that patient.

The known causes of asthma are so numerous and so varied that it has

From the Allergy Division, Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville, Virginia.

Dr. Coleman, a former Fellow in Allergy, is now associated with the Ochsner Clinic, New Orleans, La.

Dr. Pearsall, a former Fellow in Allergy, is now associated with the Mason Clinic, Seattle, Wash.

Dr. Curry, a former Fellow in Allergy, is now located in Appleton, Wisconsin.

been helpful to classify them into three groups of nine types (Table I).[2-4] Allergy and infection are the usual primary causes (Group I). Asthma due primarily to allergy or infection is commonly intensified by the five secondary types of causes (Group II). These secondary causes may be of

TABLE I. THE NINE TYPES OF CAUSES OF WHEEZING IN CHRONIC ASTHMA*

Group I. The Usual Primary Causes
- Allergy:
  - Foods, inhalants and drugs.
- Infection:
  - In nose, sinuses, throat, bronchi.

Group II. Causes Which Precipitate or Intensify Wheezing in Asthma from Allergy or Infection
- Reflex:
  - Nasal polyps, thyroid nodules, bronchial obstruction, nodules in pharynx, other.
- Physical Allergy:
  - Drafts, temperature, humidity and weather changes, wet feet, exercise in cold.
- Psychogenic:
  - "Life's situations."
- Non-specific Irritants:
  - Smokes, odors, chemicals, fresh paint, insecticides, detergents.
- Chronic Lung Diseases:
  - Emphysema, fibrosis, bronchiectasis.

Group III. Asthma as a Manifestation of other Serious Diseases:
- Cardiac Asthma:
  - Paroxysmal left ventricular failure
- Bronchial Obstruction:
  - Carcinoma of the lung, benign bronchial tumors, foreign bodies, kinks in bronchi from scars and extra-bronchial compression (cysts, mediastinal tumors).

Group IV. Idiopathic Causes

*Modified from The American Pract. & Digest of Treatment, 8:1353, 1957[3].

primary or major importance occasionally. Asthma from paroxysmal left ventricular failure (cardiac asthma)[5] or from bronchial obstruction[6] are placed in Group III. They are placed in a separate group because of their serious prognostic import and because they are important illnesses in which asthma is an additional complication. Brown and Halpin[7] have advocated a similar classification.

The study of every case of asthma in this clinic is designed to determine the presence or absence and the relative importance of allergy, infection and the other causes of asthma. The criteria by which the roles of allergy and infection are recognized are summarized in Table II. The criteria which point to the other causes of asthma are summarized in Table III. They are discussed in detail elsewhere.[2-4]

An Asthmagram is simply a tabulation of the data obtained by the use of these differential criteria under appropriate headings, as outlined in Table I. The following case report was designed to illustrate the formulation of an Asthmagram. It illustrates also (a) a method for conducting a comprehensive diagnostic survey; (b) the information sought in the history, physical, x-ray and laboratory examinations and skin tests; (c) the manner in which the 100 following cases were studied; and (d) the role of the Asthmagram in formulating a therapeutic program.

TABLE II. CLINICAL COMPARISON OF ALLERGIC (ATOPIC) AND INFECTIOUS ASTHMA*

Allergic (Atopic)	Differential Criteria	Infectious
	History	
Predictable often	Season	Cold and changeable
Late in attack	Cough	Prominent, early
No residual	Cough	Residual
Mucoid, early or late	Sputum	Purulent
Mucoid, early or late	Nasal discharge	Purulent
Foods and inhalants	Precipitating factors	Respiratory infections
Frequent	Other allergy	Infrequent
Frequent	Sneezing	Infrequent
Frequent	Itching eyes	Infrequent
Frequent	Lacrimation	Infrequent
Absent	Fever	Common
No effect	Antibacterial therapy	Shortens or aborts
Good	Response to adrenalin and aminophylline	Fair or poor
	Physical Examination	
Pale swelling	Nasal mucosa	Red, swollen
Mucoid	Nasal secretions	Purulent
Pale translucent	Uvula	Red, wrinkled
Pale	Tonsils	Red or normal
Pale	Lateral pharynx	Red streaks
Asthma	Chest	Asthma
Transilluminate	Sinuses	Often opaque
	Laboratory Data	
Clear or thick mm. symmetrical	Sinus x-rays	Opaque or hazy, often unilateral
Normal	Leukocytes	Elevated or normal
Infrequent	Eosinophillia	Common
Foods and inhalants prominent	Skin tests	Foods and inhalants not prominent

*Reprinted from the *Virginia Medical Monthly* 82:65, 1955[2].

TABLE III. SYMPTOMS AND SIGNS SUGGESTING PRESENCE OF NON-ALLERGIC, NON-INFECTIOUS CAUSES OF WHEEZING* **

History	
Dyspnea only on exertion—1, 2***	Inconsistencies—6***
Dyspnea without wheezing—1, 2	Aspiration—3, 4
Exhausting cough—2, 3	Attacks due to
Fear of death—1	Heat—5
Interval air hunger—1, 6	Cold—5
Known heart disease—1	Weather—5
Rapidly developing	Chest pain—1, 3
Debility—3	Hemoptysis—1, 2, 3
Emphysema—3	Relief by
Seeking air for relief—1	Rest—1, 2
Unilateral emphasis—3, 4	Supine—2
Asthma from smoke and odors—7	Attacks from insecticides—7
Physical Examination	
Incr. A-P diameter—2***	Asymmetrical ventilation—2, 3***
Interim cyanosis—2, 3	Faint heart sounds—2
Interim orthopnea—1, 3	Inspiratory stridor—3
Nasal polyps—4	Interim reduced exercise tolerance—1, 2
Sighing respiration—6	
Thyroid nodules—4	Left ventricular loads—1
Venous collaterals—2, 3	No wheezing in attacks—2, 6
Hyperventilation—6	Clammy hands—6

* Modified from the *Virginia Medical Monthly* 82:67, 1955[2]

** See Table VI for additional differential criteria

*** Key: 1. Cardiac asthma
2. Chronic lung disease
3. Bronchial obstruction
4. Reflex asthma
5. Physical allergy
6. Psychogenic asthma
7. Non-specific irritants

CASE REPORT

Chronic Asthma due to Multiple Causes

Clinical Data: CWS, male, age 13.

Complaint: Asthma.

Other Allergy: Perennial hay fever since first year of life.

Sequence of Events: He aspirated a chicken bone during his first year. This was followed by asthma, which subsided after removal by bronchoscopy. Asthma returned six months later, associated with a bronchial infection. It recurred four or five times each winter, with respiratory infections, for the next four years. Perennial asthma, with and without infection, developed during the past six years.

Frequency: Almost constant. *Time of Day:* Worse at night. *Months in which asthma occurs:* All. Worse in winter and spring. *Relieved by:* Routine symptomatic remedies usually, but not always. *Prodromata:* None. *Unilateral preponderance:* None. *Freedom between attacks:* Partial. *Role of Environment:* Worse since moving to present home two years ago. Asthma often relieved in air-conditioned hotel room. *Cough:* Precedes attacks and is prominent. *Nasal and bronchial discharges:* Mucoid usually. Purulent with upper respiratory infections. *Food history:* Nuts, berries and fish cause asthma. Others were suspected but not proven. *Inhalant history:* Dust, mold, and perhaps dogs, cause asthma. *Physical allergy history:* Exercise, cold and dampness cause asthma. *Psychiatric history:* Mother considered emotional factors of major importance because they caused hyperventilation and wheezing which she could relieve by gestures of affection and by diversion. His parents had separated. He was subject to periods of depression. *Family history:* Brother had hay fever and mild asthma. *Infection history:* Purulent nasal and bronchial discharges with colds. Infection was definitely associated with the severe attacks of asthma.

Physical Examination: Pale, boggy mucous membranes of nose and pharynx. Uvula enlarged and pale with translucent tip. Mucopurulent postnasal discharge and lymphoid hyperplasia in the pharynx. Right antrum opaque to transillumination. Diffuse wheezing in both lung fields.

Skin Tests: Many positive reactions to foods, pollens and other inhalants, including autogenous house dusts.

Laboratory Examination: Leukocytosis during respiratory infections, with 10 per per cent eosinophilia.

Treatment: Food and inhalant avoidance. Injections of inhalant and bacterial allergens, antibiotics, repeated lavage of right antrum, symptomatic remedies, simple psychotherapy.

Progress: Marked relief in about ten weeks. There were two exacerbations, associated with bronchial and sinus infections, which responded quickly to antibiotic therapy during the next year. Thirteen months after the initial visit, relief was estimated to be about 80 per cent. His mother was advised to continue the allergen injections.

ASTHMAGRAM

Evidence for Allergy.—Hay fever, family history positive for allergy, asthma from dust and mold, pale boggy nasal and pharyngeal membranes and uvula. Many positive skin tests, relief from allergy management. *Evidence for infection.*—Cough preceded attacks and was prominent. Much worse with upper respiratory infections. Pus lavaged from opaque right antrum. Pus in the nasopharynx. Antibiotics lessened the severity and duration of infectious attacks. *Physical allergy.*—Dampness, cold and exercise aggravate or precipitate asthma. *Nonspecific irritants.*—Smoke, fumes and the odor of fresh paint cause asthma. *Psychogenic factors.*—Worse when upset, product of a "broken home," episodes of depression, hyperventilation and mild attacks relieved by diversion and overt affection. Apparent benefit from simple psychotherapy. *Bronchial obstruction.*—Asthma followed aspiration of a chicken bone and was relieved promptly by bronchoscopic removal. *Reflex factors.*—None. *Cardiac symptoms.*—None. *Chronic lung disease.*—Equivocal.

Comment.—Once the Asthmagram was assembled, the management fell automatically into orderly channels. For example: Four types of causes of asthma played important roles, namely: allergy, infection, psychogenic factors, and bronchial obstruction. Physical allergy and nonspecific irritants played minor roles which required no specific attention. Treatment consisted of: Removal of the bronchial obstruction, routine management of allergic and infectious components (including lavage of the infected antrum) and simple psychotherapy. One year after the institution of this program, relief was estimated at 80 per cent. The disciplines of the allergist, rhinologist, bronchoscopist, and pediatrician were employed.

ANALYSIS OF 100 ASTHMAGRAMS

Asthmagrams, like the one in the case report, were made of 100 consecutive new cases of chronic asthma upon completion of their diagnostic survey. The diagnostic data were then tabulated in a master Asthmagram which was too detailed to be used here. Instead, the pertinent data have been summarized in Tables IV, V and VI. The data in Table IV are in complete accord with the long accepted belief that the conventional allergic asthma,

TABLE IV. DISTRIBUTION OF THE GROUPS AND TYPES OF CAUSES OF WHEEZING IN 100 CONSECUTIVE ASTHMAGRAMS

Cause of Wheezing	Number
Group I	
Allergy	90
Infection	73
Group II	
Physical allergy	71
Non-specific irritants	54
Chronic lung disease	31
Psychogenic	26
Reflex	9
Group III	
Cardiac	5
Bronchial obstruction	3
Total	362

ninety of the one hundred cases, is the most frequent type. Asthma from infection, seventy-three cases, was a close second. There was no significant evidence of a role of allergy in ten of these cases. In this, and in a series of 100 cases of infectious asthma, allergy plus infection seemed to cause asthma more often than either alone. The incidence of secondary roles of physical allergy 71 per cent, non-specific irritants 54 per cent, chronic lung disease 31 per cent, psychogenic 26 per cent, and reflex factors 9 per cent, was considerable. The incidence of three cases of bronchial obstruction and five cases of cardiac asthma is thought to be above average.[8]

Table V gives some idea of the relative importance of the history, skin tests, physical and x-ray examinations in the recognition of the various types of causes of wheezing. The history seemed to provide more diagnostic leads, 429, than the other examinations combined. The physical examination, the next most useful diagnostic discipline, provided 209 criteria. X-ray examinations provided eighty-three diagnostic leads. The positive skin tests in

eighty-one patients provided little differential diagnostic information. But they were invaluable aids in the recognition of offending allergens, after the role of allergy had been suggested by the Asthmagram.

TABLE V. ROLES OF THE HISTORY, PHYSICAL AND X-RAY EXAMINATIONS AND SKIN TESTS IN THE ACCUMULATION OF THE DIFFERENTIAL CRITERIA IN TABLE VI

Diagnostic Procedure	Allergy	Infection	Physical	Reflex	Chronic Lung Disease	Non-specific Irritants	Psycho-genic	Cardiac	Bron-chial Obstruc-tion
History	90	73	71	0	25	111	26	17	16
Physical Exam.	50	41	0	66	31	0	12	5	4
X-ray	0	43	0	0	31	0	0	0	9
Skin Tests	81	0	0	0	0	0	0	0	0

An outline of the master Asthmagram and a rather detailed summary of the incidence of the individual differential diagnostic criteria are shown in Table VI. Careful study of this table will show that the individual differential criteria are apt to have little diagnostic weight. A little experience with the Asthmagram will show that constellations of criteria are needed to confirm concurrent etiological roles of allergy, infection, chronic lung disease and the other types of causes of wheezing (Table I) in a case of asthma. For example, perennial mucoid sputum and nasal discharges are not acceptable evidence of allergic asthma unless they are associated with other evidence of allergy, such as positive food or inhalant histories, hay fever, cough late in the attacks, and a pale translucent uvula. By the same token, a nasal polyp merely suggests the possibility of a nasobronchial reflex, which can be confirmed only by relief of asthma following polypectomy. Similarly, an asthmatic who seeks air during an attack and has definite evidence of heart disease cannot be said to have cardiac asthma unless there are other supporting criteria[5] or he is benefited by cardiac therapy. Diagnostic constellations of criteria can be obtained readily as a rule, as shown by the data in Table VI.

The sixteen differential criteria which suggest a role of *allergy* were observed 950 times (Table VI-1) in ninety of the one hundred cases (Table IV). This is nearly twice the incidence of criteria which point to any other type of cause of wheezing.

The sixteen criteria which suggest *infection* were observed 533 times (Table VI-2) in seventy-three cases (Table IV), the second highest incidence.

The twenty-one criteria of *chronic lung disease* were recorded 249 times (Table VI-3) in thirty-one cases (Table IV).

The nineteen criteria which suggested a *psychogenic* component of asthma were recognized 119 times (Table VI-4) in twenty-six cases (Table IV).

TABLE VI. MASTER ASTHMAGRAM SUMMARY

(Incidence and distribution of differential diagnostic criteria tabulated by types of causes of wheezing)

1. Evidence of Allergy	Number
History	
Family history	63
Other allergy	71
Seasonal component	27
Perennial	94
Food history	23
Inhalant history	77
Good epineph. & ephed. relief	65
Mucoid nasal discharge	64
Mucoid sputum	62
Cough late	51
Physical Examination	
Pale mucous membranes	50
Translucent uvula	10
Sinuses normal	55
Diffuse wheezing	74
Skin Tests Positive	
Foods	79
Inhalants	85
Total	950

2. Evidence of Infection	Number
History	
Cough early and/or prominent	54
Purulent discharges	52
Precipitated by acute infections	65
Fever and/or malaise	31
Relief from antibiotics	42
Poor epineph. & ephed. relief	16
Winter emphasis	32
Physical Examination	
Red mucous membranes	45
Red uvula	29
Pus in nose or throat	36
Sinuses hazy	44
"Patchy" rales & wheezing	12
Fever	8
Laboratory	
Leucocytosis	12
X-rays positive	32
Eosinophils >5%	23
Total	533

3. Evidence of Chronic Lung Disease	Number
History	
Dyspnea without wheezing	24
Dyspnea only on exertion	13
Chronic cough without wheeze	8
Relief by rest	23
Relief by lying down	8
Sputum without asthma	10
Physical Examination	
Poor chest motions	15
Interim use of accessory muscles	8
A-P diameter increased	21
Poor diaph. motions	14
Heart sounds faint between attacks	10
Soft breath sounds	10
Systolic epig. thrust	2
Venules at the diaphragm	3
Clubbed fingers	14
Interim cyanosis	6
X-ray: Cysts	2
Fibrosis	12
Emphysema	22
Bronchiectasis	2
Abnormal lung function tests	22
Total	249

4. Evidence Suggesting Psychogenic Component	Number
History	
Verbose	13
Inconsistencies	10
Hard to "pin down"	10
Inhalant and food history unlikely	2
Nebulizer "chain smoked"	3
"Life situations"	12
Frequent sighing	4
Other psychogenic syndromes	10
Dry mouth	14
Excessive sweating of hands and feet	12
Physical Examination	
Rapid respirations	1
Dyspnea disproportionate to auscultatory wheezing	2
Panicky behavior	3
Clammy hands	11
Pupils dilated	4
Relief from placebos	0
Sedatives and/or atropine	3
Poor symptomatic response	4
Total	118

5. Evidence of Physical Allergy	Number
Aggravated or Precipitated by:	
Heat	15
Cold	25
Drafts	31
Weather changes	42
Temperature changes	37
Exercise in cold	40
Exercise in heat	33
Total	223

6. Symptoms from Nonspecific Irritants	Number
Fresh paint	16
Tobacco smoke, others	23
Tobacco smoke, own	6
Grease smoke	33
Perfume	6
Insecticides	9
Soap powders	18
Total	111

TABLE VI. MASTER ASTHMAGRAM SUMMARY

(Continued)

7. Possible Bronchial Reflex Sources	Number
Polyps	8
Thyroid nodules	1
Postnasal discharges	25
Unilateral emphasis of symptoms or signs	5
Definite bronchial obstruction	3
Granular pharynx	24
Total	66

8. Evidence for Heart Disease	Number
History	
During attacks	
Seeks fresh air	17
Palpitation++	10
Sweating++	10
Frothy pink sputum	1
Extreme suffocation	11
Fear of death	8
Left ventricular loads	1
Physical Examination	
Left ventricular loads	3
During attacks	
Pulse++	10
Blood pressure+	3
P_2+	0
Fetal or gallop rhythm	5
Cyanosis	12
Therapeutic response to:	
Digitalis	5
Oxygen	3
Tourniquets	0
Salt restriction	0
Diuretics	2
Total	101

9. Evidence for Bronchial Obstruction	Number
History	
Unilateral emphasis	5
Foreign body aspiration	0
Hemoptysis	2
Chest pain	6
Exhausting cough	11
Physical Examination	
Inspiratory stridor	2
Unequal ventilation	0
Collateral veins	1
Generalized adenopathy	1
X-ray	
Mass in lung	1
Mass in mediastinum	0
Localized	
Emphysema	5
Atelectasis	1
One diaphragm fixed	1
Total	36

The history of aggravation or precipitation of asthma by one or more of the seven *physical allergy* factors was positive 223 times (Table VI-5) in seventy-one cases (Table IV).

Seven *non-specific irritants* caused wheezing 111 times (Table VI-6) in fifty-four patients (Table IV).

Five possible sources of *bronchial reflexes* were observed sixty-three times (Table VI-7). Bilateral wheezing associated with unilateral *bronchial obstruction* was observed three times, presumably due in part to a broncho-bronchial reflex. In nine cases, relief following polypectomy (8) and nodular thyroidectomy (1) was equivocal (Table IV).

The eighteen criteria suggesting cardiac asthma were recognized 101 times (Table VI-8). But a definite diagnosis of cardiac asthma, based on relief by cardiac therapy, was made only five times (Table IV). There was a surprisingly high incidence of "seeking fresh air," marked palpitation and sweating, a sense of extreme suffocation and fear of death in non-cardiac asthma.

Fourteen criteria suggesting bronchial obstruction were recorded thirty-six times (Table VI-9). But definite bronchial obstruction was demonstrated only three times (Table IV).

DISCUSSION

These observations illustrate quite well the necessity for a detailed survey of all etiological possibilities in every case of chronic asthma. Had this not been done, the cases of bronchial obstruction, cardiac asthma and some of the cases of chronic lung disease would not have been diagnosed promptly, nor would many of the other 362 types of causes (Table IV) have been recognized.

It is common knowledge that the prime objective of a diagnostic etiological survey in asthma is directed towards the recognition of offending allergens and infections. The etiology of acute asthma, with significant periods of freedom between attacks is apt to be less varied than in chronic asthma in which wheezing occurs almost daily. In acute asthma the secondary causes of wheezing require little attention. But in a series of chronic complicated asthmatics, good results cannot be expected unless therapy is directed against each recognized cause of wheezing. By the same token, the incidence of attacks and the need for symptomatic remedies is often lessened by careful attention to the secondary causes of wheezing (Group II, Table I).

Attention has been called to the frequent need for a constellation of criteria in order to incriminate the several types of causes of wheezing. This is particularly true when one attempts to assign active roles of allergy, infection, chronic lung disease, bronchial obstruction, left ventricular failure, obscure bronchial reflexes and emotional conflicts.

A constellation of criteria is not always necessary, however. For example, nonspecific irritants, physical allergy, psychogenic factors and naso-bronchial reflexes play obvious roles in the etiology of attacks of asthma which start when a housewife fries bacon, a man walks in cold wind, a young girl is unfairly disciplined, or when asthma is relieved by removal of a nasal polyp.

Several points need to be emphasized: (1) An Asthmagram, which is made when the initial diagnostic survey is completed, can indicate only tentative roles for the various types of causes of wheezing. Final roles can be assigned only after relief has been obtained by treating the individual causes. (2) The 123 differential criteria listed in Table VI are not considered complete. Each of them should be subjected to critical evaluation by other observers. (3) The possible combinations of these criteria are almost incalculable. It is therefore impractical to attempt to compile a list of acceptable diagnostic combinations of these criteria. To circumvent this difficulty, a series of case reports has been compiled[2,3,8,9] which illustrate both the use of these criteria in the composition of an Asthmagram and the role of the Asthmagram in the formulation of therapeutic programs for the relief of asthma. They illustrate many of the common combinations of causes of asthma also. (4) The management of chronic asthma requires painstaking efforts to recognize the multiple types of causes (an average of 3.6 per case) which contribute to the morbidity of this common human affliction.

SUMMARY

Asthma is a complex syndrome which can be precipitated by many diverse causes. They have been classified for convenience (Table I) into three groups of nine types of causes, each of which puts its clinical stamp upon the syndrome. The Asthmagram is a clinical device by which the etiological information obtained in the diagnostic survey of a patient is classified into these nine types of causes of wheezing. The Asthmagram then provides an orderly approach to the management of a case of asthma. The clinical criteria by which each of the nine types of causes of wheezing can be recognized are summarized in Tables II and III.

A case report outlines the diagnostic survey of an asthma patient in this clinic and illustrates the use of the Asthmagram in formulating a therapeutic program.

The data contained in the Asthmagrams of 100 consecutive cases of chronic asthma were tabulated in a master Asthmagram. These data are summarized in three tables.

The nine types of causes of wheezing were recognized 362 times in this group of 100 cases, an average of 3.62 types of causes per case. The incidence of each recognized type of cause of asthma was as follows: Allergy —90 per cent, infection—73 per cent, physical allergy—71 per cent, nonspecific irritants—54 per cent, chronic lung diseases—31 per cent, psychogenic factors—26 per cent, potential reflex stimuli—9 per cent, cardiac asthma—5 per cent, and bronchial obstruction—3 per cent.

REFERENCES

1. Unger, L. and Wolf, A. A.: Treatment of bronchial asthma. A survey of the value of treatment in 459 cases during 20 years. JAMA, 121:325, 1943.
2. Swineford, O., Jr.: Classification and etiologic diagnosis of asthma. Virginia Med Monthly. 82:64.
3. Swineford, O., Jr.: Berger, K. W., Coleman, W. P., and Cumbia, J. W.: The asthmagram. A diagnostic approach to asthma. Amer Practit. 8:1353, 1957.
4. Swineford, O., Jr.: Asthma, classification of causes. J Allergy, 25:151, 1954.
5. Swineford, O., Jr.: Cardiac asthma. Southern Med J, 15:1387, 1960.
6. Guerrant, J. L., and Pearsall, H. R.: Reflex bronchospasm caused by localized airway obstruction. An asthma-like syndrome. Ann Allergy 18:1226, 1960.
7. Brown, E. A. and Halpin, L. P.: A tentative quantitative classification of asthma. Ann Allergy, 12:445, 1954.
8. Swineford, O., Jr., Johnson, E. R., Cook, H. M., and Ochota, L.: Infectious asthma. An analysis of the asthmagrams of 100 cases and a critical review. (In preparation for publication).
9. Swineford, Oscar, Jr.: Observations on infectious asthma. Southern Med J, 51:637, 1958.

University of Virginia (Dr. Swineford)
School of Medicine

ALLERGY TO FLEA BITES

Clinical and Experimental Observations

BEN F. FEINGOLD, M.D., F.A.C.A., and E. BENJAMINI, Ph.D.
San Francisco, California

OUR INITIAL INTEREST in flea bite reactions dates back about five years, when, in response to a number of patient requests for control of flea bites, we undertook to prepare a flea antigen.

Flea bites have always been a commonly encountered problem in the San Francisco Bay Area as evidenced by the complaints recorded by the early explorers of this region and also by the fact that the limited number of publications encountered in the medical literature have been reports by investigators from the San Francisco Bay Area. The first of such reports was by Cherney, Wheeler and Reed[1] in 1939 followed by the observations of McIvor and Cherney[2,3] in 1941 and 1943, and finally the reports of Hatoff[4] and Hartman[5] in 1946, and Lunsford[6] in 1949.

In each instance, except for the experience reported by Hartman with histamine azo-protein, desensitization or hyposensitization was attempted using extracts of whole fleas. The results recorded varied. Some enthusiastically reported successful treatment, while others reported poor results. An unfortunate factor in the work documented has been the dependence of the observers on subjective reports from patients regarding both the insect causing the clinical symptoms and the patient's response to treatment. However, many patients never see the insect which bites them except in the case of mosquitoes and biting flies. With secretive insects such as fleas and bed bugs, an individual may possibly be bitten for years without noticing the insect, and in addition, what appears to be the offender may not be accurately identified. During our observations, individuals have brought to the clinic what they considered to be fleas, but proved to be anything from saw-tooth grain beetles to small seeds. Under such uncontrolled conditions it would be (1) difficult to ascertain whether clinical lesions are actually due to flea bites, and (2) when hyposensitization is attempted, whether the freedom from bites should be attributed to the treatment or rather to a cessation of flea activity. Since flea populations undergo marked seasonal fluctuations, it is quite possible that reported relief of patients could have been due to a decline in local flea populations.

Presented in part at the Seventeenth Congress of The American College of Allergists, Dallas, Texas, March 15-17, 1961.

The investigations were supported by Research Grant E-1389 from the National Institute of Allergy and Infectious Diseases of the National Institute of Health, U. S. Public Health Service.

Dr. Feingold is Chief, Department of Allergy, Kaiser Foundation Hospitals, Northern California, and, Director, Laboratory of Medical Entomology, Kaiser Foundation Research Institute.

Dr. Benjamini is Assistant Director, Laboratory of Medical Entomology, Kaiser Foundation Research Institute.

McIvor and Cherney for example reported that of a total of ninety-two patients given a six weeks' course of treatment, sixteen stated that bites were fewer in number, seventeen stated that the bites were less severe, forty-three reported that bites were less severe and fewer in number, while five reported no benefit and one claimed the bites were more severe. It appears doubtful that hyposensitization to flea bite reactions would result in fewer bites (that is, the repelling of the insects or the inability of fleas to bite successfully).

In order to determine the nature of the hypersensitive response and the allergen responsible for the bite reaction, we proceeded to gather clinical and laboratory information from controlled experiments dealing with flea bite hypersensitivity. The purpose of this report is to present the information so far obtained.

Recognizing the need for the large numbers of fleas required for both the preparation of antigens and testing of patients under our proposed program, the initial step was the development of techniques for the mass rearing of fleas. Such techniques were successfully developed in our laboratories and reported in 1958 in the *Bulletin of the World Health Organization.*[7,8] Currently, we are rearing approximately 1,000,000 cat fleas *Ctenocephalides felis felis (Bouche)* per month, and small quantities of human fleas *Pulex irritans L.*

For our studies of flea bite sensitivity, three species of laboratory-reared fleas were used. These were the cat flea, *Ctenocephalides felis felis,* and the human flea, *Pulex irritans,* both of which were implicated through our epidemiological studies as the primary agents causing flea bite reactions in the San Francisco Bay Area. *Pulex simulans Baker,* a flea of the native gray fox variety which according to Smit[9] is closely related to *Pulex irritans,* was included for comparative purposes. It was found that *Pulex irritans* could not be reared in numbers sufficient for the production of antigen, while *Pulex simulans,* a closely related species could be reared on the fox in quantities adequate for our studies.

Fleas for experimental purposes were collected one to two days after emergence from the pupal stadium. No flea used had access to animals or blood meals of any type previous to clinical use. After collection fleas were used for (1) testing patients and animals, and (2) the preparation of antigens.

Testing for the Flea Bite Reaction.—For testing purposes, the individual fleas were placed in clear plastic containers ¾-inch deep and 1 inch in diameter, which were covered on one end with nylon chiffon gauze. These containers were then placed, gauze-covered surface down, on the flexural surface of the forearm of the subjects to be tested. The cages were removed after fifteen minutes and the skin surface inspected for evidence of biting activity. The bites were usually evidenced by small punctations. In those cases in which feeding was not apparent, the fleas were examined under a microscope for evidence of a blood meal. If no feeding had

occurred, this test was repeated using a fresh flea and a different skin area. After testing, all fleas were discarded, no flea being used for more than one test. Observations of the resulting reactions were taken twenty minutes and twenty-four hours following the application of the flea. In some cases, observations were continued every day for a period of one to two weeks. The phenomena recorded were erythema, whealing, induration (papules), vesiculation and bullae.

Since a definite cross reactivity was observed for the various species of fleas used, it was decided to concentrate our studies on the reactivity to the cat flea together with periodic testings of *P. irritans* and *P. simulans* reactivity.

THE BITE REACTION[10]

In humans the initial lesion was marked by a punctate hemorrhagic area representing the site of probing by the insect. Appearing almost immediately around the probe site was a wheal with or without accompanying erythema. The wheal reached its peak in approximately five to thirty minutes. In very few instances (twelve per cent) the whealing reaction, accompanied by itching, cleared leaving no residual except for the punctate area. In most instances (about 88 per cent of the immediate whealing reactions) there was a gradual transition to an indurated papular lesion which reached its full development within twelve to twenty-four hours. In about 63.2 per cent of the bite reactions, the delayed reaction appeared within twelve to twenty-four hours, with no preceding whealing reaction. In these instances the lesion was fully developed within twenty-four to seventy-two hours. At times, small vesicles were superimposed on the base of a papule while in some cases vesicles, or more rarely even bullae, were observed rather than papules. Frequently the delayed lesions persisted for one to two weeks or even longer.

The lesions occurred in clusters. All lesions were confined to the skin area covered by the cage. Since no lesions were observed outside this circumscribed area, it was concluded that the multiple lesions were not local manifestations of a systemic reaction caused by a single feeding puncture, but that each lesion was the response to a separate probing by the flea. During the stages preliminary to feeding, the fleas generally explored the complete skin area exposed. During this search, the flea would frequently stop and probe the skin surface. This probing, without feeding, appeared sufficient in itself to account for the development of lesions at each site. No case was noted in which exposure to a single flea caused the development of generalized urticaria as reported by Lunsford[6] and Hartman.[5]

Pruritus was present with each type of lesion. As the evanescent wheal absorbed, pruritus disappeared, so that the whealing lesion was rarely a subject of complaint. However, pruritus increased in intensity as the papule developed, so that the common lesion of complaint was the delayed papular reaction. This was the lesion that brought the patient to the clinic.

TABLE I. HUMAN RESPONSE TO BITES OF *PULEX IRRITANS, CTENOCEPHALIDES FELIS FELIS* AND *PULEX SIMULANS*

Number of Tests	Negative	Reactors	Immediate Only	Both Immediate and Delayed	Delayed Only	Total Delayed
			Response to *P. irritans* bites			
90	25 27.8%	65 72.2%	1 1.5%*	27 41.5%*	37 57.0%*	64 98.5%*
			Response to *C. felis felis* bites			
84	41 48.8%	43 51.2%	3 7.0%*	11 25.5%*	29 67.5%*	40 93.0%*
			Response to *P. simulans* bites			
95	37 39.0%	58 61.0%	4 6.9%*	15 25.9%*	39 67.2%*	54 93.1%*

*Per cent of total reactors

Tables I and II summarize the observations made on all humans tested during the first phase of our studies. In these tables reactions have been classified as either immediate or delayed. Of a total of 269 individual tests, ninety were performed with *Pulex irritans;* eighty-four with *Ctenocephalides felis felis,* and ninety-five with *Pulex simulans.* Only eight immediate reactions without subsequent delayed reactions were observed. In fifty-three tests an immediate reaction was followed by a delayed reaction, and in 105 instances only a delayed reaction without a preceding immediate response was observed. The total number of delayed reactions was 158 or 95.2 per cent of the total cases reacting.

TABLE II. IMMEDIATE AND DELAYED RESPONSES OF HUMANS TO FLEA BITES

Number of Tests	Negative	Reactors	Immediate Only	Total Immediate*	Immediate and Delayed	Delayed Only	Total Delayed*
269	103	166	8	61	53	105	158
	38.3%	61.7%	4.8%**	36.8%**	32.0%**	63.2%**	95.2%**

*including those showing immediate and delayed
**Per cent of total reactors

These observations served to emphasize early in our studies that the delayed reaction was the important response to flea bite reactivity and also indicated that a relationship seemed to exist between the immediate and the delayed reaction.

That a relationship does exist between the immediate reaction and the delayed reaction has been reported for other types of insect bites.

In 1946 Mellanby[11] reported that previously unexposed human subjects following periodic bites of the mosquito *Aedes aegypti* present the following sequence of skin reactions: first there is a short period in which no reaction is exhibited. Following this initial induction period, the subjects

exhibit a delayed inflammatory reaction which is gradually supplanted by an immediate wheeling reaction, which in turn fades as the periodic exposure continues. The complete spectrum of reactions may take as long as a year or more. An identical response has been reported by Theodor[12] for individuals exposed to the bites of sand flies *(Phlebotomus* sp.).

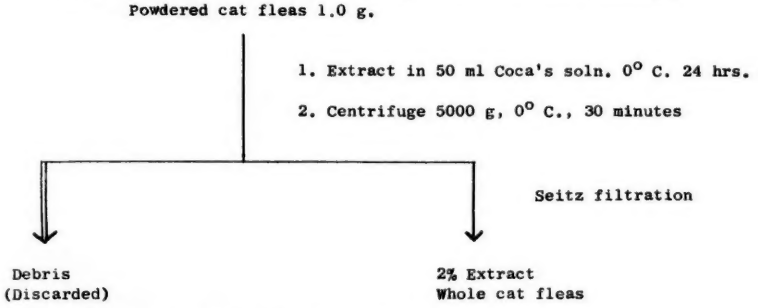
A similar sequence of skin reactivity in humans has been reported by Mote and Jones[13] following the periodic intradermal administration of rabbit serum, and by Simon and Rackemann[14] following the administration of guinea pig serum. In 1958 Salvin[15] working with toxoids in guinea pigs, found that after intradermal injections of very small dosages of diphtheria toxoid, a short induction period of two to three days was followed by a period of delayed inflammatory reaction, which in turn was supplanted by an immediate wheeling reaction. He reported that as the toxoid dosages were decreased, the period of delayed reactivity was extended.

We shall refer to this phenomenon again in our discussion of experimental observations.

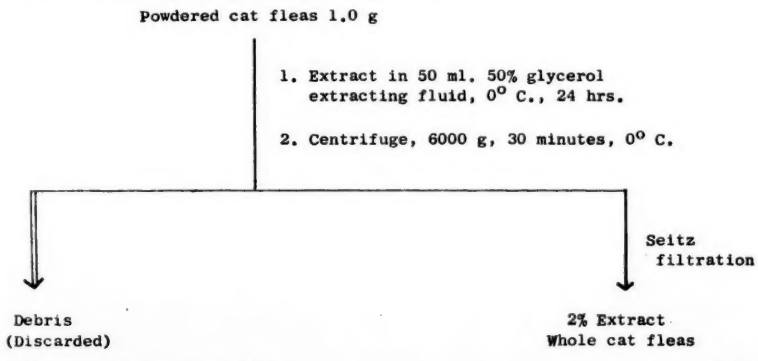
TESTING WITH ANTIGENS

Antigens were prepared from cat fleas, according to the following techniques:

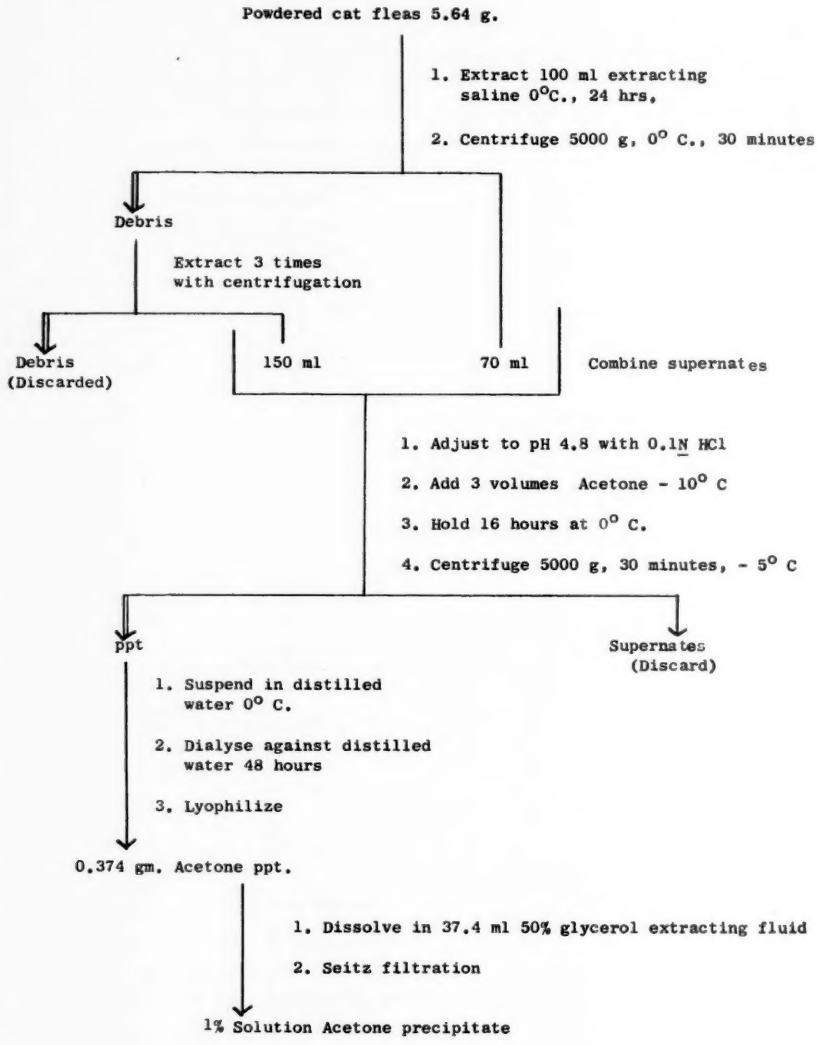
A. WHOLE FLEA EXTRACT (according to McIvor and Cherney[2])



B. WHOLE FLEA EXTRACT (50% glycerol)

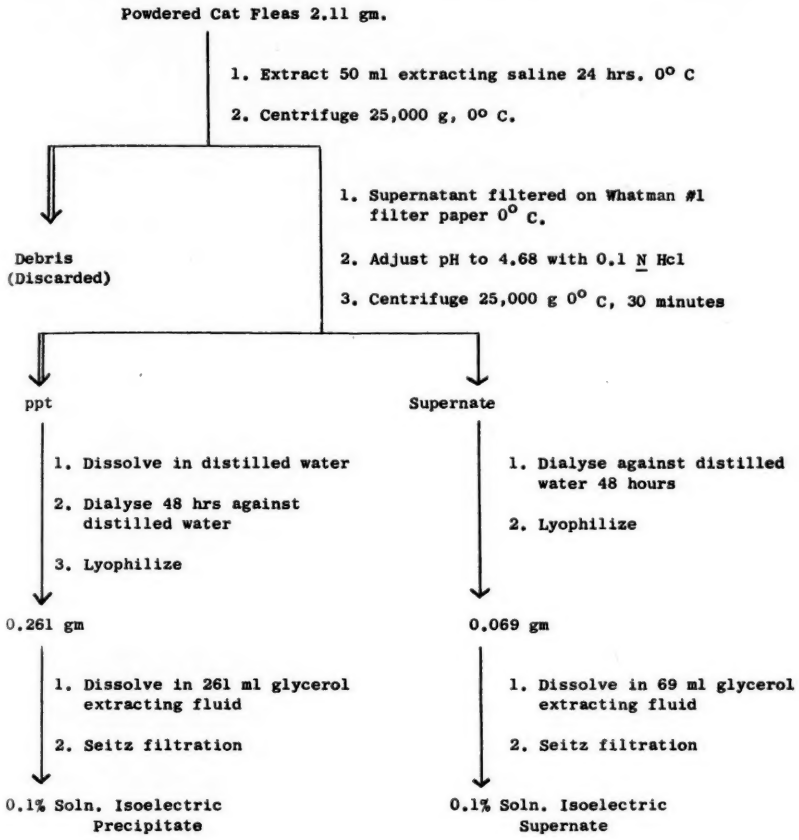


C. Acetone Precipitation



From the tests of flea bite reactive patients, a definite correlation was observed for the delayed reaction to flea bites and the delayed reaction to antigens. No such correlation could be demonstrated for the immediate response. When delayed lesions were induced by the intradermal injection of antigens, the delayed lesions corresponded to the delayed reaction to

D. Isoelectric Separation of Cat Flea Antigens



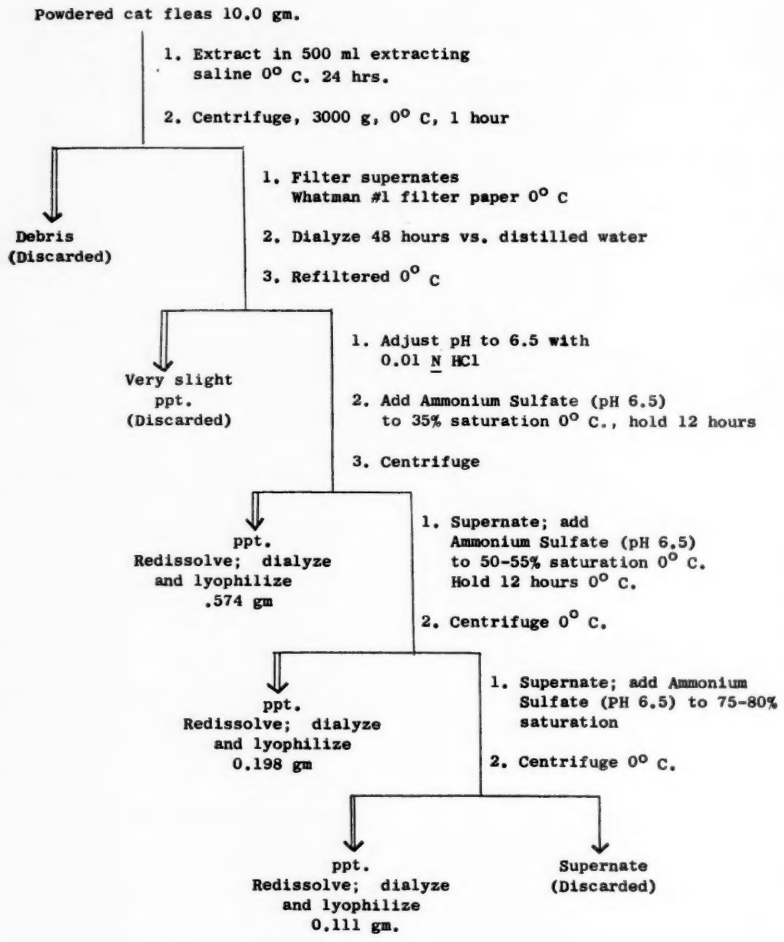
cat flea bite with respect to the time of appearance of the lesion, and its morphology.

DESENSITIZATION WITH WHOLE FLEA ANTIGENS

In order to evaluate hyposensitization with whole flea extract, a group of thirty-one patients who showed positive reactions when tested with *P. irritans* and *C. felis* were administered cat flea antigens subcutaneously at by-weekly and weekly intervals for periods varying from five to twenty-five months.

The concentration of the maintenance dosage of the antigen varied from 1:5,000,000 W/V to 1:50 W/V. In no instance did the volume exceed 0.4 cc when concentrations below 1:50 were used, and never in excess of 0.25 cc for concentrations of 1:50.

E. Salt Fractionation of Cat Flea Antigens



After periods of treatment varying from five to twenty-five months the patients were again challenged with fleas (*C. felis* and *P. irritans*) reared in our insectary.

In no case did the response to the challenging bites show an improvement over the original challenge before treatment was started. In every instance the reaction was either the same as before the course of treatment or, as was observed in the majority of patients, the degree of reactivity was actually increased. In some cases the degree of reactivity was the most violent observed in all our testing experience. Extensive whealing followed by vesiculation

was observed in several patients who previously manifested slight initial erythema followed by papules. This experience was contrary to the favorable reports of previous investigators, who based their results upon subjective experiences related by the patients.[2,3]

EXPERIMENTAL OBSERVATIONS

Our clinical observations impressed us with the importance of the delayed type of reaction in flea bite sensitivity and indicated a correlation between the immediate and delayed types of reactivity. The observations of other investigators with other insects such as the mosquito, sand fly, etc., emphasized a definite sequence of events with regard to skin reactivity. The latent period followed by a delayed reaction and then an immediate reaction followed by failure to react could not be definitely correlated in our clinical observations. The individual phases of such a spectrum were observed in the human (Table I), but the complete pattern was not confirmed. Added to these clinical observations was the experience, common to both laymen and professionals, that many subjects eventually fail to respond to flea bites. That information is as old as history. With the clinical data at hand for flea bite reactions, we were so far unable to reconstruct the pattern which investigators suggest for the bites of other insects such as mosquitoes and sand flies. To add to our problem in testing with antigens derived from whole bodies of fleas, we could correlate the delayed reaction resulting from intradermal injection of antigens and those resulting from the actual flea bite, but not the immediate reaction. Facing these difficulties we undertook to study the problem in animals.

Sensitization of Animals with Flea Bites.[16,17]—Our initial laboratory experiments consisted of sensitizing guinea pigs to flea bites by daily exposure to fleas. In general we observed that the delayed skin reaction appeared from five to seven days after initial exposure to flea bites and developed within twelve to twenty-four hours after the bite. If the animal was exposed to daily flea bites, no reactions appeared until the fifth to seventh day of exposure. In these instances of daily exposure, in approximately 30 per cent of the animals, there was a flare-up of all the previous bite sites. It is conceivable that the so-called generalized urticaria following insect bites, reported by clinicians, is merely a flare-up of previously non-reacting sites.

If exposure to flea bites was continued beyond the period of delayed reactivity, the animals developed immediate reactions appearing within thirty minutes to one hour following exposure. The immediate reactions in each instance developed into papules which persisted for days. The immediate reactions appeared within two to five days following the appearance of the delayed reactions. It is important to point out that the delayed reaction seems to be a prerequisite for the development of immediate reactivity in flea bite sensitivity. The immediate reaction in guinea

pigs appears only after the development of the delayed reaction. On the other hand, when rabbits were sensitized by flea bites, the stage of delayed reactivity was completely absent. The immediate reaction appeared within ten to fourteen days.

The sequence of reactivity observed in the guinea pig clarifies the clinical observation recorded in Tables I and II. In humans, the predominance of the delayed reactions in 158 instances out of a total of 166 bite reactions corresponds with the experimental observation in guinea pigs in that the delayed reaction typifies the basic response to the flea bite. The experimental observation that the immediate reaction is a sequel to the delayed response tends to confirm the correlation between the immediate reactivity and delayed reactivity observed clinically in sixty-one instances or 36.8 per cent of the bite reactions. It is likely that in humans the eight instances of immediate reaction not followed by delayed lesions were manifestations of the atopic type. Such reactions for insects and insect parts have been reported by other investigators.[18-21] On the other hand, it is possible that these instances represent cases already in later stages of the reactivity syndrome.

In order to determine whether sensitization is systemic or local, we sensitized animals with flea bites in one area of the body, and after the usual induction period of five to seven days, we challenged a different region of the body. Positive reactions were observed upon such challenge indicating a generalized systemic sensitivity rather than a localized or contact type.[17]

Sensitization of Animals with Antigen.[17]—Having successfully induced sensitivity to flea bites by fleas in animals, we proceeded to correlate such sensitivity with antigens prepared from the whole flea body.

Antigens used were prepared by saline extraction of ground defatted fleas followed by the dialysis and lyophilization of the extract.

Attempts to sensitize guinea pigs by intramuscular or subcutaneous injections of whole flea extract in saline resulted in failure, but guinea pigs could be successfully sensitized by either the intramuscular injection of whole flea extract in combination with a complete Freund's adjuvant, or by the intradermal injection of whole flea extract in saline.

A further correlation between flea bite sensitivity and whole flea extract was demonstrated by the positive reaction of flea sensitized animals to a challenge with 0.05 ml of 1 mg/ml whole flea extract. At the end of twenty-four hours, a delayed reaction was observed.

Sensitivity induced by intradermal injection of whole flea extract in saline requires a longer latent period of ten to fourteen days as compared with five to seven days when induced by actual flea bites. We offer no explanation to account for the difference. Systemic sensitization was confirmed by experiments with whole flea extract.

The separation of the whole flea extract into major protein fractions by

electrophoresis and by precipitation with ammonium sulfate at various degrees of saturation revealed that some of the fractions obtained by either separation could induce hypersensitivity to flea bites, suggesting that the active principle was in these fractions. The correlation between the electrophoretic mobilities of the fractions obtained by both methods of separation suggested that the fractions obtained by one method were the same as those obtained by the alternative method.

Immunological Studies.—Attempts to demonstrate precipitating antibodies in sera of guinea pigs, sensitized to flea bites by bites of fleas, were unsuccessful. However, low titers (maximum 1:80, ranging from negative to an exceptional 1:160) were demonstrated by hemagglutination, using rabbit RBC partially digested with trypsin and using either *in vitro* collected oral secretion of fleas or whole flea extract as the antigen. When obtained, titers were always with sera of guinea pigs at the stage where delayed reactions were accompanied by immediate reactions or at the stage of immediate reactivity only. Detailed results of the immunological tests will be reported elsewhere.

Studies with Flea Oral Secretion.[23]—Although an active principle responsible for flea bite skin reaction was demonstrated in both whole flea extract and fractions thereof, it was considered advisable to study the actual oral secretion injected by the insect.

The general assumption has been that insect oral secretion is responsible for skin reactivity in insect bites. Until recently such an hypothesis was not substantiated. In 1960, Hudson, Bowman and Orr[22] reported that after severing the salivary duct of a mosquito, the bite of the insect was not followed by a skin reaction. Similar evidence did not exist for the flea.

We undertook the collection and study of flea oral secretion in order to demonstrate that the secretion contains a substance capable of inducing sensitivity and subsequent skin reactivity and also to make this material available in as pure a form as possible.

The oral secretion of laboratory bred cat fleas was collected *in vitro* in distilled water. Approximately 1,000 fleas were confined in each feeding chamber. The insects were permitted to feed for one hour on distilled water at 37° C through a highly purified animal membrane ("Silverlight"*). At the end of the feeding period the substrate was collected and lyophilized. The lyophilized product was green-brown in color and had a somewhat gummy consistency. The feeding of about 100,000 fleas yielded approximately 100 micrograms. The product was then taken up in 15 ml of saline and filtered through an ultrafine glass filter to remove bacterial contamination. Controls consisted of identical distilled water collection and treatment but with no fleas in the feeding chamber. Upon lyophilization the control flask was colorless with no detectable yield.

*"Silverlight" membrane, Julius Schmid, Inc., New York, New York.

Guinea pigs received two intradermal injections of 0.5 ml of oral secretion in saline at weekly intervals. For intraperitoneal injections, the animals received 0.15 ml of oral secretion either in saline or combined with Freund's complete adjuvant.

TABLE III. RESULTS OF PRELIMINARY CHEMICAL AND BIOLOGICAL TESTS ON THE *IN VITRO* COLLECTED ORAL SECRETION OF THE CAT FLEA

Proteins	−
Amino acids	+
Peptides	+
Sugars—low molecular	+
Sugars—high molecular	−
Nitroso compounds	−
Polyhydric alcohols	+
Aldehydes	+
Phenols	+
Phosphates	+
Reducing substances	+
Ketones	+
Diastase	−
Protease	−
Lipase	−
Spreading activity	+
Anticoagulatory properties	−

Two weeks following the initial injection each animal was challenged daily with the bites of twenty fleas until delayed reactions appeared.

The animals injected with oral secretion in saline failed to develop sensitivity, but the secretion in combination with Freund's complete adjuvant induced sensitivity. The latter operation indicates that oral secretion contains a substance capable of inducing sensitivity in the animal but without the aid of an adjuvant the secretion was inactive in this respect.

We further observed that oral secretion, injected intradermally into an animal sensitized with flea bites, manifested delayed reaction. From these observations we reasoned that the oral secretion does contain an active principle capable of inducing sensitivity and capable of reacting in a sensitized animal, but that the substance was perhaps an incomplete antigen or a hapten.

The Chemical and Biological Activity of In Vitro Collected Oral Secretion of the Cat Flea.—Results of preliminary chemical and biological tests on the *in vitro* collected oral secretion of the cat flea are summarized in Table III. Details will be published in future communications.

The failure to demonstrate proteins or high molecular weight carbohydrates in the oral secretion by chemical means lends support to the thesis that the active principle in the *in vitro*-collected oral secretion which is responsible for the bite reaction is haptenic in nature.

The possible haptenic nature of the active principle may help to explain our failure to achieve desensitization with whole flea extract.

As we have pointed out earlier, following continued exposure to insect bites individuals do fail to react. This has been demonstrated for mosquitos in humans, and recently we have succeeded in attaining a state of nonresponsiveness in guinea pigs and dogs. Guinea pigs exposed twice weekly to large numbers of fleas (20 or 200 at a single challenge) will develop the characteristic cycle of reactions, that is, an incubation period of five to seven days, followed by delayed reactivity, then immediate reactivity, followed by a failure to react to periodic exposures for about four months. We are still observing these animals to determine if and when reactivity recurs.

A veterinary surgeon, in collaboration with our laboratory, has observed that dogs which are carefully groomed are subject to flea bite reactions and dermatitis. Mongrel dogs infested with fleas show no skin reactivity. We have had in a number of dogs treated by exposure to fleas and by means of intradermal injection of flea oral secretion a successful induction of nonreactivity.

DISCUSSION

The allergic nature of the reaction to flea bites has been demonstrated experimentally in guinea pigs by (1) the induction of sensitivity to flea bites by exposure to flea bites; (2) the injection intramuscularly of whole extract combined with Freund's complete adjuvant; (3) by the intradermal administration of whole flea extract in saline; and (4) by the intraperitoneal injection of oral secretion combined with Freund's complete adjuvant. These observations seem further to confirm that the active principle responsible for flea bite reactions is contained in both whole flea extract, and oral secretion. In each instance sensitivity was demonstrated by a challenge with the actual flea bite.

The sensitivity induced was of the delayed type. When immediate reactions did appear in response to flea bites in guinea pigs, they were part of a delayed hypersensitivity response. In this respect, the immediate reactions observed with hematophagous insects, such as fleas, differ from the anaphylactic type of immediate response induced by Hymenopterous or stinging insects. This differentiation in the nature of the immediate response to the bites of biting and stinging insects helps clarify our clinical observations.

Although several investigators as Mote and Jones,[13] Salvin,[15] Simon and Rackeman,[14] have demonstrated a similar correlation of immediate and delayed reactivity, the exact relationship of these phenomena to the classical tuberculin response and the arthus mechanism awaits further investigation for clarification.

The demonstration that the hypersensitivity response to flea bites may be associated with a haptenic mechanism raises several problems to be answered. One of these problems is the nature of the role of the skin in the induction of the hypersensitivity pattern observed. The failure to induce sensitivity with whole flea extract in saline, except by the intradermal route,

suggests that the skin may play a role in the sensitization mechanism. Our failure to induce sensitivity in animals following the intradermal injection of saline containing *in vitro* collected oral secretion of the flea would indicate that either the *in vitro* collected oral secretion is lacking some component secreted during the *in vivo* bite, or else that the method of injection in some way differs from the natural injection by the flea.

The indication of a haptenic mechanism would further serve to explain our failure, as well as that of other investigators, to hyposensitize with whole flea extract. This failure can probably be explained by the fact that the hapten present in whole flea extract is already conjugated, resulting in a complete antigen which can sensitize the individual. With continued administration of whole flea extract, sensitivity is actually enhanced. This could explain the increased reactivity observed in our patients following the administration of whole flea extract.

Protection against sensitivity to a hapten has been demonstrated experimentally by Chase.[24] We have successfully protected guinea pigs and dogs from flea bite hypersensitivity by continued massive exposure to flea bites and also by intradermal injection of oral secretion. The fact that individuals lose their reactiveness after continued exposure to biting insects is common clinical knowledge.

The use of the flea and perhaps other biting insects can serve as an excellent tool for studying hypersensitivity of the delayed type. Our continued observations will be concerned with the nature of the sensitizing agent involved in the flea bite reaction, the possible role of the host's skin in the sensitizing mechanism and the fate of the antigen in the animal. Through such observations we hope that not only will the answer to control of insect bites be found but that also a clearer understanding of the mechanism of delayed hypersensitivity tissue response will be achieved.

ACKNOWLEDGMENT

The studies on the preparations of antigens were initiated by Bruce Hudson, Ph.D., who is presently associated with the San Francisco Field Station, Technology Branch, C.D.C., U.S.P.H.S., San Francisco, California.

The authors wish to express their sincere thanks to Dr. L. Kartmen, Senior Scientist, San Francisco Field Station, C.D.C., U.S.P.H.S., for his advice and interest in the studies, to Messrs. M. Shimizu, Harry F. Noller Frank P. de Buren and Eddi Benjamini for their technical assistance, to Miss Florence Owyang for her clinical assistance and to Miss Margaret Dempster for editorial assistance.

REFERENCES

1. Cherney, L. S., Wheeler, C. M., and Reed, A. C.: Flea antigen in prevention of flea bites. Amer J Trop Med, 19:327, 1939.
2. McIvor, B. C., and Cherney, L. S.: Studies in insect bite desensitization. Amer J Trop Med, 21:493, 1941.
3. McIvor, B. C., and Cherney, L. S.: Clinical use of flea antigen in patients hypersensitive to flea bites. Amer J Trop Med, 23:377, 1943.
4. Hatoff, A.: Desensitization to insect bites. JAMA, 130:850, 1946.

5. Hartman, M. M.: Flea bite reactions: Clinical and experimental observations and effect of histamine-azoprotein therapy. Ann Allergy, 4:131, 1946.
6. Lunsford, C. J.: Flea problem in California. Arch Dermat & Syph, 60:1184, 1949.
7. Hudson, B. W., and Prince, F. M.: A method for large scale rearing of the cat flea, *Ctenocephalides felis felis* (Bouche). Bull WHO, 19:1126, 1958.
8. Hudson, B. W., and Prince, F. M.: Culture methods for the flea *Pulex irritans (L.)* and *Pulex simulans (Baker)*. Bull WHO, 19:1129, 1958.
9. Smith, F. G. A. M.: A preliminary note on the occurrence of *Pulex irritans (L.)* and *Pulex simulans (Baker)* in North America. J Parasit, 44:523, 1958.
10. Hudson, B. W., Feingold, Ben F., and Kartman, L.: Allergy to flea bites. II. Investigations of flea bite sensitivity in humans. Exp Parasit, 9:264, 1960.
11. Mellanby, K.: Man's reaction to mosquito bites. Nature, 158:554, 1946.
12. Theodor, O.: A study of the reaction of *Phlebotomus* bites with some remarks on "Harara." Trans Roy Soc Trop Med Hyg, 29:273, 1935.
13. Mote, J. R., and Jones, T. D.: The development of foreign protein sensitization in human beings. J Immun, 30:149, 1936.
14. Simon, F. A., and Rackemann, F. M.: The development of hypersensitiveness in man following intradermal injection of antigen. J Allergy, 5:439, 1934.
15. Salvin, S. B.: Occurrence of delayed hypersensitivity during the development of Arthus type hypersensitivity. J Exp Med, 107:109, 1958.
16. Hudson, B. W., Feingold, Ben F., and Kartman, L.: Allergy to flea bites. I. Experimental induction of flea bite sensitivity in guinea pigs. Exp Parasit, 9:18, 1960.
17. Benjamini, E., Feingold, Ben F., and Kartman, L.: Allergy to flea bites. III. The experimental induction of flea bite sensitivity in guinea pigs by exposure to flea bites and by antigen prepared from whole flea extracts of *Ctenocephalides felis felis*. Exp Parasit, 10:214, 1960.
18. Feinberg, A. R., Feinberg, S. M., and Benaim, Pinto C.: Asthma and rhinitis from insect allergens. I. Clinical importance. J Allergy, 27:437, 1956.
19. Perlman, F.: Insects as inhalant allergens—Consideration of aerobiology, biochemistry, preparation of material and clinical observations. J Allergy, 29:302, 1958.
20. Wiseman, R. D., Woodin, W. G., Miller, H. C., and Myers, M. A.: Insect allergy as a possible cause of inhalant sensitivity. J Allergy, 30:191, 1959.
21. MacLaren, W. R., Eisenberg, Ben C., Frank, D. E., and Kessler, J.: Reactions to Insect Allergens. The incidence of response to testing among allergic and non-allergic persons. Calif Med, 93:224, 1960.
22. Hudson, A., Bowman, L., and Orr, C. W. M.: Effect of absence of saliva on blood feeding by mosquitoes. Science, 131:1730, 1960.
23. Benjamini, E., Feingold, Ben F., and Kartman, L.: Antigenic property of the oral secretion of fleas. Nature, 188:959, 1960.
24. Chase, M. W.: Interference with induction of the anaphylactic state by prior feeding of a hapten-like allergenic chemical. Fed Proc, 8:402, 1949.

2425 Geary Boulevard, San Francisco, California.

WHOSO DESIRETH TO MAKE TRIAL

Whoso desireth to make trial of the same experiments, let him handle the substances, not negligently and carelessly, but prudently, deftly and in the proper way; nor let him (when a thing doth not succeed) ignorantly denounce our discoveries: for nothing hath been set forth in these books which hath not been explored and many times performed and repeated amongst us.—WILLIAM GILBERT (1544-1603). From *De Magnete, London*, 1600 (Basic Books, New York, 1958).

CLINICAL EVALUATION OF CINNARIZINE (MITRONAL®) IN VARIOUS ALLERGIC DISORDERS

BENJAMIN ZOLOV, M.D., F.A.C.A.
Portland, Maine

THE SEARCH for new antihistaminic compounds has continued at an active pace for the past fifteen years. Not only is the safety factor of major importance, but also clinical potency and lack of side effects are constantly considered in the treatment of our allergic patients. All of us are aware that, to date, the more effective compounds produce a major degree of sedation and a lesser degree of nausea, vertigo, and other side effects.

This study of 100 unselected allergic patients from office and clinical practice reveals the new antihistamine cinnarizine (Mitronal®) to be clinically effective and remarkably free from undesirable side reactions.

PHARMACOLOGY

Cinnarizine*, N-benzhydryl-N'-cinnamylpiperazine, is a white crystalline powder soluble in dilute mineral acids but relatively insoluble in water. Studies in animals indicate[1] potent antihistaminic activity, approximately 3 mg/kg being sufficient to protect 50 per cent of a group of guinea pigs from histamine aerosol-induced bronchospasm. Reflex behavior and hypnotic activity, along with blood pressure and respiration, remained within normal limits in laboratory animals.

ACUTE AND CHRONIC TOXICITY

Acute Toxicity. No deaths occurred[1] in mice given 1280 mg/kg of cinnarizine orally. This was the largest amount of the compound which could be mechanically administered to the animals.

Chronic Toxicity. To determine chronic toxicity, thirty young growing rats were studied[1] for twelve weeks. Fifteen of these animals served as controls and fifteen were given a daily oral dose of 50 mg/kg of cinnarizine, a dosage which represents approximately two hundred times the expected human therapeutic dosage. Weekly determination of body weights and growth curves for each group were not significantly different. After completion of the experiment, histopathologic investigation was carried out on the brain, heart, lungs, liver, spleen, kidneys, bone marrow and muscles. No consistent histological differences were found between the treated and control groups.

Dr. Zolov is Chief of Allergy Clinic and Senior Attending Physician, Maine Medical Center.

Presented at the Seventeenth Annual Congress of The American College of Allergists, Dallas, Texas, March 15, 1961.

*The cinnarizine used in this study was supplied as Mitronal® by the G. D. Searle & Co., Chicago, Illinois.

EVALUATION OF CINNARIZINE—ZOLOV

METHOD OF STUDY

This study began in October, 1960, progressed through February, 1961, and included eight hayfever patients who were given the drug earlier in the pollen season. A previous larger study outlined below will deal with the results obtained from the pollen sensitive patients who were treated with Mitronal® during the pollen seasons. One hundred patients ranging from six months to sixty-nine years of age were included in this series. Both tablets and syrup were used. The average dosage in children was 20 mg daily while in adults the average daily dosage was 75 mg. However, twenty-eight patients were maintained on dosages of 100 mg to 200 mg of Mitronal® daily. Each patient took the drug for at least five days, while the longest period was four months.

This series included patients undergoing hyposensitization as well as those on standard acute allergic management. Most of them had tried other antihistamines which proved unsatisfactory, many causing annoying side effects. Several had been taking corticosteroids with return to symptoms on withdrawal. *Mitronal® was not given to patients who were controlled satisfactorily with other drugs.* There were no significant blood pressure changes noted. Blood studies were not done routinely, but no dyscrasia was noted in those cases in which they were carried out.

REVIEW OF LITERATURE

Barrett and Zolov[2] reported on the clinical evaluation of 255 allergic patients with the use of Mitronal,® covering a one year period, from October, 1959 through September, 1960. That particular series included patients ranging in age from seven months to eighty years. The drug was used in syrup and tablet form, the average dosage in children being 20 mg daily while the average dosage for adults was 40 mg daily. In that group 41 per cent showed excellent results, 24 per cent good results and 18 per cent had poor results. Of fifty-three pollen sensitive patients, nineteen obtained no relief.

The most consistent relief appeared in patients with chronic urticaria and in those with pruritus due to other skin diseases. The drug was effective in children with bronchial asthma, but showed little efficacy in adult asthmatics. Only 8 per cent of the patients had side effects and these usually disappeared or were alleviated by simple adjustment in dosage. There was no evidence of any circulatory complications or blood dyscrasia noted in that series.

Wahner and Peters[3] tested Mitronal® at the Mayo Clinic with four other newer antihistamines and reported no side effects in a small group. Trumbull[4] et al found Mitronal® effective against seasickness in a study of 221 patients. Philipszoon[5] reported on fifty-five cases of dizziness and found Mitronal® effective in the majority of cases with true vertigo. No alteration of the blood picture was seen in eight patients who received the drug for more than six months.

Schiller[6] reported on eighty patients with hayfever. Only 15 per cent of the subjects failed to obtain amelioration of symptoms. Rather prominent were the insignificant number of side effects. Nine patients complained of drowsiness, one had a headache and one dryness of the throat. Proper drug adjustment was made, and in no case was it necessary to discontinue Mitronal.®

CASE STUDIES

Case 1. A sixty-five-year-old male patient, first developed angioedema of his upper lip, followed by generalized urticaria after an attack of the grippe in January, 1953. For the next eight years he was afflicted with chronic hives and lip edema almost daily. He was given all types of antihistamines, put on special diets, and finally required short term steroid hormone therapy to obtain some relief. He had a known allergy to aspirin and penicillin which were carefully avoided. All the skin tests were negative. Extremes of cold and heat often aggravated his symptoms. In September, 1960, he was started on Mitronal® 40 mg daily. After two weeks of therapy, his symptoms entirely disappeared. In December, 1960, following a sore throat, during which he was inadvertently given penicillin by another physician, he developed a severe relapse of angioedema of his lips. Another course of Mitronal® 40 mg daily, for a ten day period, completely controlled his symptoms. Occasional hives are now relieved with Mitronal® 10 mg daily.

Case 2. A ten-year-old boy developed vasomotor rhinitis in March, 1956, complicated by bronchial asthma six months later. His first bout of asthma did not respond to standard treatment, and he required a three week course of cortisone to control his symptoms. Over the next five years he grew progressively worse, particularly during the colder months. He lived on Tedral, four to six daily, Aminophyllin suppositories, and in addition, required short term steroid hormone therapy for relief. Antibiotics were given on many occasions with attacks complicated by respiratory infections and fever.

Skin tests revealed a dust and mold allergy for which he received hyposensitization on a perennial basis along with a stock bacterial antigen. With the exception of steroid hormones, no other drugs effectively controlled his symptoms for a period longer than two weeks.

In January, 1961, he was started on Mitronal® 50 mg daily in divided doses. At the end of one week's therapy he was gradually taken off prednisone which he had been taking in daily doses up to 10 mg for the previous two weeks. He has been remarkably free of symptoms for the past two months on the 50 mg daily dosage of Mitronal.® He takes one Tedral occasionally to supplement his present therapy.

RESULTS

The results of this five-month study are shown in Table I. From these findings it would appear that Mitronal® has proven quite effective in many cases of allergic nature, while producing a minimum of side effects. In thirty-seven cases of vasomotor rhinitis, excellent results were obtained in sixteen patients; eleven had good results, and no relief was experienced by ten patients. Again, as in a previous study, asthmatic children had a good to excellent response in all cases with the exception of one infant who could not tolerate the drug. In adult asthmatics Mitronal® was of no benefit.

TABLE I. RESULTS OF MITRONAL® THERAPY IN 100 PATIENTS

Diagnosis	Number of Patients	Excellent (Complete Relief)	Good (Nearly Complete Relief)	Poor (Little or No Relief)	Number of Patients with Side Reactions
Vasomotor rhinitis	37	16	11	10	1
Hayfever	8	5		3	
Bronchial asthma	19	3	7	9	2
Nasal polyps	1			1	
Total	65	24	18	23	3
Angioedema or urticaria	14	13		1	
Atopic dermatitis	6	3	1	2	1
Contact dermatitis	5	2	1	2	
Erythema multiforme	1		1		
Idiopathic purpura	1	1			
Neurodermatitis	5		2	3	1
Seborrheic dermatitis	1			1	
Total	33	19	5	9	3
Miscellaneous	2		2		
Total	2	0	2	0	0
Total	100	43	25	32	6

TABLE II.
COMPARISON OF RESULTS WITH MITRONAL® IN ADULTS AND CHILDREN

Diagnosis	Number of Patients		Relief					
			Excellent		Good		Little or None	
	Adults	Children	Adults	Children	Adults	Children	Adults	Children
Vasomotor rhinitis	32	5	14	2	10	1	8	2
Hayfever	7	1	4	1			3	
Bronchial asthma	11	8	1	2	2	5	8	1
Nasal polyps	1						1	
Angioedema or urticaria	13	1	11	1	1		1	
Atopic dermatitis	3	3	2	1		1	1	1
Erythema multiforme	1				1			
Contact dermatitis	5		2		2		1	
Idiopathic purpura	1		1					
Neurodermatitis	5				2		2	1
Seborrheic dermatitis	1						1	
Miscellaneous	2		1				1	
Total	82	18	36	7	18	7	27	5

TABLE III. INCIDENCE OF SIDE EFFECTS IN 100 PATIENTS

Diagnosis	Total Number of Patients	Total Number of Patients with Side Reactions	Drowsiness	Nausea, Vomiting, or Both	Diarrhea	Gastric Acidity	Xerostomia
Vasomotor rhinitis	37	1				1	
Bronchial asthma	17	2	2				
Erythema multiforme	1	1			1		
Atopic dermatitis	6	1		1			
Neurodermatitis	6	1*	1				1
Hayfever							
Nasal polyps							
Angioedema or urticaria							
Contact dermatitis							
Idiopathic purpura							
Seborrheic dermatitis							
Total	100	6	3	1	1	1	1

*Patient reported two side effects.

Those patients with chronic dermatitis often had relief from pruritus—even though the rash remained unchanged.

The most amazing results were seen in cases of angioedema and urticaria, no matter what etiology was found.

Only one patient failed to obtain any relief out of fourteen urticarial patients.

SIDE EFFECTS

Three patients developed drowsiness taking the drug; included in this group was one patient who also developed a dry tongue. One patient complained of heart burn, while there was one case each of vomiting and diarrhea. In only two cases was it necessary to discontinue the drug because of the above symptoms. Reduction of dosage controlled the side effects in the others. One two-year-old child accidentally swallowed eight 5 mg tablets without any harm. It is comforting to report that in this series of 100 cases the percentage of Mitronal® reactions, compared to other antihistamines, was amazingly small.

SUMMARY AND CONCLUSION

A clinical evaluation of cinnarizine (Mitronal®) in 100 cases showed excellent results in 43 per cent, good results in 25 per cent and little or no improvement in 32 per cent. The most persistent relief was obtained in cases of angioedema and urticaria. The drug was most effective in children with bronchial asthma, while adult asthmatics showed no particular response to the drug. There was no evidence of circulatory complications or blood dyscrasia noted. Only 6 per cent of the patients had side effects, and these disappeared by simple dosage adjustment.

Every physician is aware of the enthusiasm with which many patients accept a new drug. However, whenever possible, objective findings were thoroughly evaluated with the patients in this series.

It was most comforting to know that side effects rarely became a problem with the use of Mitronal.®

This drug will find a proper and effective place in the field of allergy. Good, comprehensive therapy with antihistamines, diets, hyposensitization and even steroids are necessary to control the allergic individual. Mitronal,® the safe antihistamine with few side reactions, provides us with an excellent drug to reach this goal.

REFERENCES

1. Unpublished data, Division of Biological Research, G. D. Searle & Co.
2. Barrett, R. J., Jr., and Zolov, B.: A clinical evaluation of cinnarizine (Mitronal®) in various allergic disorders. J Maine Med Ass 51:454 (Dec) 1960.
3. Wahner, H. W., and Peters, G. A.: An evaluation of some newer antihistaminic drugs against pollinosis. Proc Mayo Clin 35:161 (March 30) 1960.
4. Trumbull, R., et al.: Effect of certain drugs on the incidence of seasickness. Clin Pharmacol & Therap 1:280 (May-June) 1960.
5. Philipszoon, A. J.: Influence of cinnipirine on dizziness. Ned Geneesk (in press).
6. Schiller, I. W.: A clinical assessment of N-benzhydryl-N'-cinnamyl-piperazine (cinnarizine) in seasonal allergic rhinitis. J Maine Med Ass 51:359 (Oct) 1960.

296 Congress Street

CLINICAL EVALUATION OF BRONKOTABS

A New Anti-Asthmatic Drug Combination

WILLIAM H. LIPMAN, M.D., F.A.C.A.
Kenosha, Wisconsin

THE PURPOSE of this paper is to report our clinical findings in a series of asthmatic patients who were treated with a new antiasthmatic drug combination. Each Bronkotabs®* tablet contains: Ephedrine sulfate, 24 mg; Theophylline, 100 mg; Thenyldiamine HCl, 10 mg; Clyceryl guaiacolate, 100 mg; Phenobarbital, 8 mg.

Several investigators have used ephedrine containing preparations—with or without the addition of sedatives, vasodilators, and expectorant agents—with fair to excellent results. Among these have been Spielman[1] who employed Bronkotabs in a series of forty patients and obtained good results in 60 per cent of his cases. Waldbott[2] reported "excellent", "very good", and "good" results with Bronkotabs in forty-one out of sixty-four patients. Other authors, including Brown, Rudolph, Clein, Bickerman, et al,[3-8] have also used phenobarbital, ephedrine, and theophylline compounds with good results in their asthmatic cases. However, a number of authors have found that the addition of an expectorant and an antihistamine to the above combination enhances the effectiveness of the sedatives and vasodilator drugs. The retained bronchial secretions, acting as obstructive agents, not only narrow the tubes but increase bronchospasm and cough. Hence, the use of expectorants in removing retained bronchial exudate and mucous improved the effectiveness of the other agents. In addition, the antihistamine drug was a useful agent in the management of many hay fever as well as asthma patients.

The use of glyceryl guaiacolate as an efficient expectorant has been confirmed by such workers as Connell,[9] Perry and Boyd, Cass and Frederick,[10-11] and Schwartz.[12] These investigators found that expectoration was freer and easier with its use with no unpleasant side effects. Schwartz rated it more effective as a mucolytic agent than potassium iodide in the treatment of bronchial asthma.

Classification of Patients and Treatment

Our group included 121 patients ranging from five months to eighty-four years of age (Table I).

Of these, sixty-one were male and sixty were female. These were divided into three clinical groups: (1) Acute Bronchial Asthma (infective or allergic)—92, (2) Persistent Bronchial Asthma—5, (3) Chronic Intermittent Bronchial Asthma—29. Ninety-three of the group had previously been

*Bronkotabs® is the registered trademark of Breon Laboratories, Inc., New York, New York.

under allergic management, in addition to receiving such supplementary conventional treatment as antihistamines, antibiotics, et cetera; 108 of these had definite histories of allergy; and 82 had additional histories of frequent upper respiratory tract infections. In addition to specific hyposensitization for their specific allergies, and antibiotic agents where indicated, this group was treated with Bronkotabs as follows (with the addition of steroids in a number of instances as well as with supplementary conventional therapy).

TABLE I. AGE DISTRIBUTION OF PATIENTS TREATED WITH BRONKOTABS
(121 Patients)

Ages	Number	Male	Female
0- 1 year	3	2	1
1-10 years	8	5	3
10-25 years	24	11	13
25-50 years	46	22	24
50 and over	40	21	19
Total	121	61	60

The three infants up to one year of age were given fifteen drops of the Elixer of Bronkotab four times a day. One teaspoonful of the Elixer contained the equivalent of the drugs in one tablet. In two of the three infants, oral liquid antibiotics were given because of the associated acute infection. Patients from one to ten years of age received twenty drops to one teaspoonful of the Elixer of Bronkotab four times a day. Three of the eight also received oral antibiotics. The remainder of the patients received one half to one tablet every four hours during the day time. Specific allergic therapy was continued in ninty-three patients on Bronkotabs, and of these forty-five required intermittent oral steroid therapy to supplement the relief of symptoms during the episodes of acute "colds" only. In these cases, oral steroids were not continued for more than a few days (usually three to four days only). In five of the longstanding cases of unrelieved asthma, oral steroids were given for periods up to several weeks and gradually withdrawn, since Bronkotabs alone were unable to keep these asthmatic patients free of clinical symptoms. We labeled our results in these patients as "poor". However, when we combined the steroids with the Bronkotabs, more satisfactory results were obtained in these five patients than with the use of either drug separately.

Of the 121 Bronkotabs-treated patients, fifty-two had *previously* been under treatment with three other efficient theophylline compounds: Tedral —thirty-one cases, Amesec—twelve cases, and Amodrine—nine cases. Previously, and in some cases simultaneously, these fifty-two patients also had specific allergic management. Of this group of thirty-one previously treated Tedral cases, twenty-six stated they had better relief with Bronkotabs; five were "about the same" or "better" with Tedral. Of the twelve previously treated Amesec cases, seven "felt better" with Bronkotabs, and two, "the

TABLE II. REVIEW OF 121 PATIENTS TREATED WITH BRONKOTABS

Ages (Years)	Number of Patients	Response to Treatment with Bronkotabs			Side Reactions to Bronkotabs					
		Good	Fair	Poor	Nausea	Nervousness	Weakness	Palpitation	Headache	Urinary Retention
0-10	11	7	3	1	2	0	0	0	0	0
10-25	24	15	6	3	2	1	1	1	0	1
25-50	46	25	11	10	3	2	2	1	1	0
50-over	40	20	13	7	1	2	1	0	0	0
Totals	121	67	33	21	8	5	4	2	1	1

Total side reactions—21 per cent.

TABLE III. REVIEW OF 52 PATIENTS PREVIOUSLY TREATED WITH TEDRAL OR AMESEC OR AMODRINE

Ages (Years)	Number of Patients	Response to Treatment with Tedral, Amesec or Amodrine			Side Reactions					
		Good	Fair	Poor	Nausea	Nervousness	Weakness	Palpitation	Headache	Urinary Retention
0-10	6	4	1	1	2	0	0	0	1	0
10-25	18	10	2	6	3	1	2	1	0	0
25-50	19	10	3	6	3	2	1	2	1	0
50-over	9	5	1	2	3	0	1	1	0	1
Totals	52	29	7	15	11	3	4	4	2	1

Total side reactions—25 per cent.

TABLE IV.
COMPARISON OF RESULTS IN PERCENTAGES

Bronkotabs			Combined Results of Use of Tedral, Amesec, Amodrine		
Response	Number	Per Cent	Response	Number	Per Cent
Good	67	55.4	Good	29	55.7
Fair	33	27.3	Fair	7	13.5
Poor	21	17.3	Poor	15	34.7

same." Of the nine previously treated Amodrine cases, eight were "more comfortable" with the "new medicine" Bronkotabs. When asked what they meant by "better", the patients stated that their tightness and wheezing were more promptly relieved and that they could "cough" easier and "get the stuff up" easier. These assertions were confirmed by us in our clinical observations on hospital cases. Forty-five of the fifty-two patients previously treated with Tedral, Amesec, or Amodrine, reported an increased and easier expectoration with the Bronkotabs.

Tables I-IV review the results of treatment of the 121 patients with Bronkotabs.

The response to treatment with Bronkotabs was most favorable in the younger age groups. In the 0-10 years age group, ten of eleven patients had good to fair results. Only two side reactions occurred. In the

10-25 age group, twenty-one out of twenty-four had good to fair results with side reactions in only six instances, (nausea, weakness, and palpitation occurring in one patient). In the 25-50 age group treated with Bronkotabs, thirty-six out of forty-six patients had good to fair relief of symptoms (with side reactions in ten cases). In the 50-and-over age group, thirty-three out of forty had good to fair relief, but side reactions occurred in only four instances.

In the review of the 52 patients previously treated with one of the theophylline compounds (either Tedral, Amesec, or Amodrine) before Bronkotabs were used, the results are significant.

In the 0-10 years age group, five out of six patients had good to fair results with three side reactions. In the 10-25 age group, twelve out of eighteen had good to fair results with seven side reactions (two in one patient). In the 25-50 age group, thirteen out of nineteen had good to fair results, with nine side reactions. In the 50 and over age group, six out of nine had good to fair responses to treatment and the number of side reactions was six.

Let it be said that our criteria for "good" results were: Complete relief of symptoms within thirty to ninety minutes. Cases were labeled "fair" when partial or complete relief occurred in one to two hours after medication with Bronkotabs. Patients requiring over two hours to obtain even partial relief or having no relief were classified as "poor" results.

This review of our results with Bronkotabs would appear to confirm the favorable clinical responses obtained by previous investigators. While it is conceded that double blind technique would have been more valuable for this evaluation, this was not possible or practical because of certain difficulties in our type of private ambulatory and hospital practice. Long and intimate knowledge of these private patients together with careful observation of these people and a most searching and critical analysis of their statements lends a satisfactory validity to our results.

SUMMARY AND CONCLUSION

1. A new antiasthmatic drug formulation, Bronkotabs, is described and the clinical studies of a group of 121 patients on this drug is reviewed and evaluated.

2. Another group of patients, treated with Tedral, Amesec, and Amodrine, was studied and the results of treatment were reviewed for comparative purposes.

3. A clinical review of the results with the two groups of drugs suggests that the addition of the glyceryl guaiacolate expectorant and the antihistamine to the new combination tablet and elixer increases the benefits to a group of asthmatic patients.

4. Side effects appear to occur less frequently with the new combination than with a group of three other drugs (Tedral, Amodrine, Amesec).

5. Of the Bronkotab-treated patients, 82 per cent had good to fair results

as compared to 69 per cent of the theophylline compounds treated group of patients, and 17 per cent of the Bronkotabs treated group had poor results as compared to 34.7 per cent of the group treated with Tedral, Amodrine, and Amesec.

6. The drug is of least benefit to the long-standing persistent asthmatic patient.

7. The drug combination (Bronkotabs) is a good addition to our armamentarium of antiasthmatic drugs and a satisfactory supplement to specific allergic management of seasonal and non-seasonal allergic rhinitis, bronchitis, and asthma.

REFERENCES

1. Spielman, A. D.: Evaluation of a combination tablet of theophylline, ephedrine sulphate, phenobarbital, thenyldiamine and glyceryl guaiacolate in the treatment of chronic asthma. Ann Allergy, 18:281 (March) 1960.
2. Waldbott, G. L.: Bronkotabs—a new antiasthmatic preparation. Int Arch Allergy, 17:116, 1960.
3. Brown, E. A.: A new type of medication to be used in bronchial asthma and other allergic conditions. Preliminary Note. New Engl J Med, 223:843, 1940.
4. Rudolph, J. A.: The symptomatic treatment of asthma. Med Rec, 150:282, (Oct 18) 1939.
5. Clein, N.: Pediatric treatment of allergic diseases. Northw Med, 49:192, (March) 1950.
6. Bickerman, H. A., Beck, G. J., Itkin, S., and Drimmer, F.: The evaluation of oral bronchodilator agents in patients with bronchial asthma and pulmonary emphysema. Ann Allergy, 11:301 (May-June) 1953.
7. Sheldon, J. M., Lovell, G. B., and Mathews, K. P.: Management of bronchial asthma in the aged. Geriatrics, 9:193, (May) 1954.
8. Scherr, M. S.: The bronchial asthmatic patient and a new therapeutic mixture. Ann Allergy, 16:247 (May-June) 1958.
9. Connell, W. F., Johnston, G. M., and Boyd, E. M.: On the expectorant action of resyl (glyceryl guaiacolate) and other guaiacols. Canad Med Ass J, 42:222, (March) 1960.
10. Perry, W. F., and Boyd, E. M.: A method for studying expectorant action in animals by direct measurement of the output of respiratory tract fluid. J Pharmacol Exp Ther, 73:65, 1941.
11. Cass, L. J., and Frederick, W. S.: Comparative clinical effectiveness of cough medication. Amer Practit, 2:844, 1951.
12. Schwartz, E., Levin, L., Leibowitz, H., and McGuinn, J. P.: The use of antitussives in the management of bronchial asthma. Amer Practit, 7:585, 1956.

625 57th Street

EXPERIMENTAL METHOD

Two things must, therefore, be considered in the experimental method: (1) The art of getting accurate facts by means of rigorous investigation; (2) the art of working them up by means of experimental reasons, so as to deduce knowledge of the law of phenomena. We said that experimental reasoning always and necessarily deals with two facts at a time: observation, used as a starting point; experiment, used as conclusion or control. In reasoning, however, we can distinguish between actual observation and experiment only, as it were, by logical abstraction and because of the position in which they stand. —CLAUDE BERNARD, *Introduction to the Study of Experimental Medicine*, tr. by H. C. Greene, 1927.

BIO-ASSAY OF FOOD ALLERGENS

I. Statistical Examination of Daily Ranges of the Human Heart Rate as Influenced by Individually Incompatible Foods

ALSOPH H. CORWIN, Ph.D., MARAVENE HAMBURGER and FRANCIS N. DUKES-DOBOS, M.D.

Baltimore, Maryland

IN MANY cases of food allergy, serological and skin tests fail. A reliable procedure for the bio-assay of food allergens should involve measurements of some physiological variable which could be analyzed by statistical methods. Coca's pulse acceleration method[1] satisfies this criterion. However, it was based upon clinical observations only, and before his method can be adopted for objective assay, several pertinent questions must be answered. For example: (1) In a given individual, are the accelerations which are caused by incompatible foods statistically significant or are they within the limits of normal variation of the daily pulse range? (2) How consistently is the ingestion of an incompatible food accompanied by pulse acceleration in a given individual and in a population? (3) Does this pulse reaction occur similarly in laboratory animals? (4) Is this pulse acceleration a consequence of antigen-antibody reaction, either direct or indirect, or is it produced by other physiological or psychological mechanisms?

Examination of the literature on human pulse rates shows that there are two different phenomena connected with eating which have not always been carefully distinguished. The first of these is an immediate increase in heart rate occurring within seconds after the start of eating which may subside within minutes after the discontinuance of eating. This is illustrated in a cardiotachogram made in our laboratories (Fig. 1). The second is a slower acceleration which may start five to ninety minutes after eating and may persist for some hours. Both phenomena are illustrated in Figure 2. We may distinguish these as the rise simultaneous with eating and the rise subsequent to eating.

Observations of the human pulse rise subsequent to eating began with the introduction of the "pulse watch" by Sir John Floyer[2a] over 250 years ago. These observations were confirmed numerous times during the nineteenth and early twentieth centuries. These early records also emphasize the importance of the temperature of food on the pulse rate.[2b,3,4]

From the Chemical Laboratories of The Johns Hopkins University, Baltimore, Maryland.

Dr. Corwin is Professor of Chemistry; Mrs. Hamburger is Research Assistant and Dr. Dukes-Dobos is a Research Associate.

This study was supported in part by a research grant, RG-3752, from the Institute of Allergy and Infectious Diseases, U. S. Public Health Service, and in part by Contract No. DA18-405-CML-606 of the Army Chemical Corps.

With the introduction of their cardiotachometer, Boas and Goldschmidt[5a] observed the heart rise of 10-20 beats simultaneous with eating and they distinguished it from the subsequent rise of 2 to 36 beats per minute after eating. They also stated, "The nature of the food consumed, as well as its temperature, must be carefully noted." In spite of this they did not present any analysis of the effect of the specific foods upon the acceleration of heart rate.

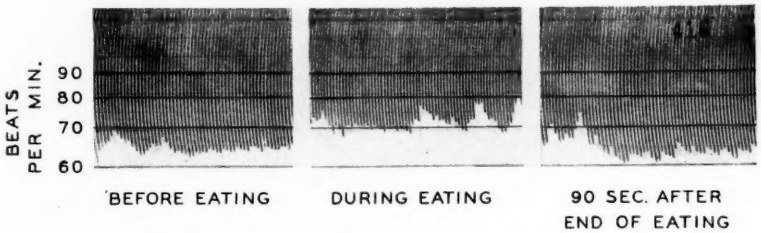


Fig. 1. Cardiotachogram showing acceleration of heart during eating. Chart Rate 1 mm/sec.

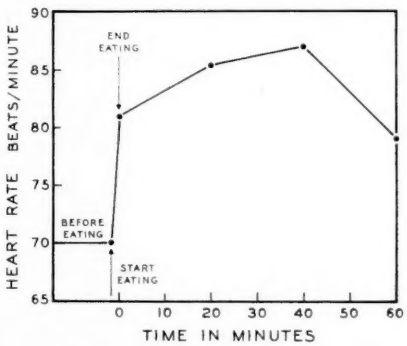


Fig. 2. Tachycardia due to specific food. Transcribed from electrocardiogram.

Beginning in 1943 Coca[6] presented a series of clinical observations on the relationship between individual foods and inhalants and pulse accelerations. In a group of 104 individuals free from infections[1a] he attempted to eliminate pulse accelerating substances from the diet and environment in order to arrive at an estimate of the "normal" pulse rate. All pulse readings were taken by palpation in the resting state. He requested fourteen observations per day for a period ranging from a few weeks to several months.[1b]

The length of time required for such observations is an obvious drawback. In spite of this, confirmations of Coca's results are beginning to ap-

pear in the clinical literature.[7-12] Hence a systematic examination of his methods and conclusions is desirable. The present paper will not attempt to relate Coca's findings to the problem of allergy but will review them critically by statistical methods with respect to the "normal" pulse, thus directing attention mainly to the first question proposed above, that is, what is the statistical significance of the pulse accelerations found by Coca?

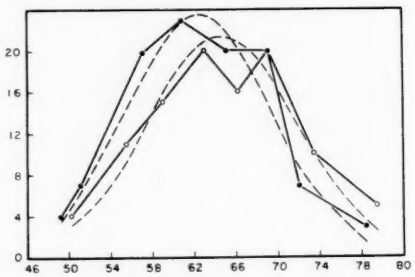


Fig. 3. Distributions of Coca's Daily Pulse Minima. o——o Before Treatment. •——• After Treatment. - - - - Normal Distribution Curves. Ordinate, Beats per Minute. Abscissa, Number of Cases.

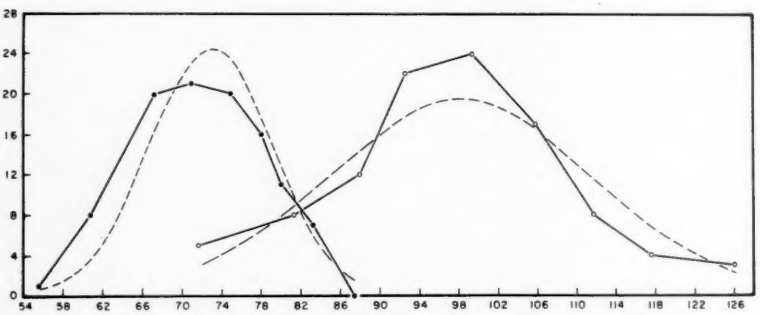


Fig. 4. Distributions of Coca's Daily Pulse Maxima. o——o Before Treatment. •——• After Treatment. - - - - Normal Distribution Curves. Ordinate, Beats per Minute. Abscissa, Number of Cases.

Coca's Observations.—Coca's group of 104 cases presents a sufficient sample for many analyses by the methods of small sample statistics. He tabulated his observations in two sets. The first set contains pulse readings taken before dietary controls were completed, the "before treatment" set. Treatment consisted in the removal of pulse-accelerating foods from the diet and the avoidance of pulse-accelerating inhalants in the atmosphere. The second set is composed of pulse readings taken after this was accomplished. Pulses were observed by the subjects themselves on the following schedule: once on arising, once on retiring, once before each meal and

three times after each meal at half-hour intervals. The table records the daily minimum and the daily maximum pulse rate in each set, giving four data for each person examined, namely, the daily low before treatment, the daily high before treatment, the daily low after treatment and the daily high after treatment.

TABLE I. LIMITS OF PULSE READINGS

	Daily Maxima		Daily Minima	
	Before Treatment	After Treatment	Before Treatment	After Treatment
Ave.	98.3	73.0	64.6	62.4
s	13.4	6.2	7.4	6.9
Ave.+2s	125.1	85.4	79.3	76.1
Ave.−2s	71.4	60.6	49.8	48.7

RESULTS OF STATISTICAL ANALYSIS

Distribution of the Data.—We have submitted each of Coca's four categories to a chi square test to find its fit to a normal distribution curve. This is important because satisfactory fit to the normal distribution curve indicates random sampling, that is, the absence of bias in the selection of data. It also indicates that the sample size is sufficient for the application of ordinary statistical methods. If the fit were not satisfactory, we should be required to seek causes for deviation such as sampling errors or other systematic bias. The theoretical and observed curves are shown in Figures 3 and 4.

These curves show a satisfactory fit to normal distribution. This conclusion is confirmed by the statistical analysis. The probabilities of fit given by the chi square test are above 0.50 for the lows before and after treatment. For the highs before and after treatment, they were 0.30 and 0.20, respectively. Since probabilities above 0.1 are accepted as showing satisfactory fit,[13] these probabilities indicate that the data presented are from a satisfactorily random sampling.

Statistical Significance of Pulse Changes.—Using the statistical methods of Fisher[13] and assuming that a significant difference would be twice the standard deviation, Table I shows that there has been no significant decrease in the daily minimum rates by Coca's avoidance treatment but that there has been a highly significant decrease in the daily maxima. This indicates that treatment by avoidance of individually incompatible foods and inhalants is successful in achieving a significant change in the high pulse readings. This shift is recorded graphically in Figure 4.

Normal Ranges.—Figure 5 is a diagram showing the correlation between the low readings and the high readings on individuals after treatment. The relatively small scatter of the points shows that the correlation is high; that is, the person who has a slow heart rate in the morning tends to have a

lower daily maximum than the person who has a fast heart rate in the morning. The statistical analysis confirms this conclusion. The numerical data are: Number of pairs, 104; standard deviations: lows, ± 6.36; highs ±6.14. The correlation coefficient, r, is 0.86 ± 0.03. Probability of lack of correlation, < 0.001.

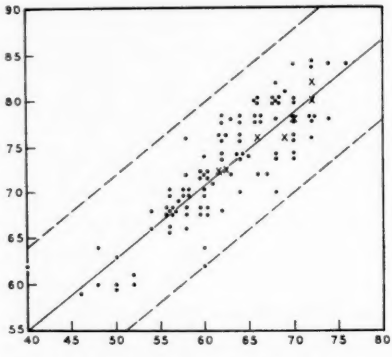


Fig. 5. Correlation between Daily Minima (x) and Daily Maxima (y) in Beats per Minute on 104 Patients after Treatment.

TABLE II. STATISTICAL PATTERN OF DAILY PULSE RATES RELATIONSHIP BETWEEN MINIMA (X), MAXIMA (Y) AND DAILY RANGES

x	$y-2s_y$	y	$y+2s_y$	Daily Ranges
50	56	63	70	6 to 20
55	60	67	74	5 to 19
60	64	71	78	4 to 18
65	68	75	81	3 to 16
70	72	79	85	2 to 15
75	76	83	89	1 to 14

The central line of Figure 5 is the line of regression. If its angle were 45 degrees from the horizontal, this would mean that the daily maximum would increase as fast as the daily minimum and the daily range would stay constant. As shown, the angle is less than 45 degrees, indicating that the ranges of the daily pulse narrow as the low readings increase (see also Table II). The extreme limits of the maxima which would encompass about 95 per cent of the cases with a given minimum reading are shown by the dashed lines.

The crosses in Figure 5 represent daily pulse ranges on seven individuals whom Coca[1b] concluded were spontaneously free from food and inhalant sensitivities. These values were not used in the calculation of the line of regression. It can be seen that they adhere to it closely. This suggests that the conclusions drawn from Coca's treated patients also apply to an untreated "normal" group.

The line of regression was obtained by the method of least squares. The calculated slope is 0.783 ± 0.003, corresponding to an angle of 38° 5′. The intercept is 24.14 ± 0.13. We may round these values and take the equation for the line as, $y = 24 + 0.78x$. The standard deviation of y, s_y, is ± 3.44. Using this equation we obtain the values given in Table II. In this table, the column "y" gives the average daily maximum for a person with a low of "x." The value "s_y" is the standard deviation of "y," so that the column "$y\text{-}2s_y$" is the lower limit of the high reading to be expected when the minimum is "x," while the column "$y + 2s_y$" is the higher limit of the high reading when the minimum is "x." These extremes encompass about 95.5 per cent of all cases. The corresponding ranges between the daily low and daily high are given in the last column. All values are rounded to the nearest integer.

TABLE III. COMPARISON OF PULSES BY SEXES

	Before Treatment				After Treatment			
	Highs		Lows		Highs		Lows	
Sex	M	F	M	F	M	F	M	F
n	48	55	48	55	48	56	48	56
Average	96.8	99.5	64.0	65.1	72.3	73.6	62.2	62.5
P	0.9		0.9		0.9		0.9	

Sex.—Earlier workers have recorded significant differences in pulse averages between males and females, although Zuntz[14] states that there is no characteristic effect of the menstrual cycle on the pulse rate. Harris and Benedict[15] obtained an average "basal" pulse of 62.26 ± 6.73 for males and 68.76 ± 9.44 for females. Boas and Goldschmidt[5c] obtained values which agreed closely. In neither case was a sustained effort made to record the pulse of each individual over a period of time.

Later observers have found no significant differences between males and females. Thus Bowerman and Brett,[16] in an investigation of 30,000 persons insured in the U.S.A. and Canada found an average of 74.7 for men and 75.8 for women. It has been suggested[16] that the relatively lower rates for women today may be due either to the more athletic, outdoor life of modern women or to a diminution in the nervousness which was possibly present at earlier examinations.

Coca's observations before treatment differ in one essential point from those of the earlier investigators, that is, they are not random samplings on individuals but are the subjects' self-recordings of the highest and lowest resting pulses found over an extended period. In the group before treatment, the lowest readings are not always "basal" since it was not always found that the lowest pulse was observed on rising.[1d] In the group after treatment an additional difference appears, that is, a consistent effort was made to eliminate foods and inhalants which caused the pulse to accelerate.

Again the readings were continued over a period of time. The data concerning sex differences are summarized in Table III.

Since P, the probability of the observations belonging to the same population, is high, we conclude that Coca's data show no significant differences between sexes. This also is the conclusion reached by Coca[1e] without statistical calculation.

Possible Sources of Error.—Since Coca's study represents the first and, to date, the most sustained effort to evaluate the effect of specific foods and inhalants on pulse rates, a statistical examination for possible sources of error was made with the special objective of diminishing standard deviations of future studies of the kind which may be made. In particular, the influence of three factors, emotion, duration of observations and number bias, has been evaluated with respect to possible counting errors.

COUNTING ERRORS

1. *Emotion.*—The necessity of having each person record his own pulse, imposed by the frequency of counts required and by the long period of time required for the completion of each set of observations, opens the way to counting errors. Several observers have postulated pulse acceleration under emotional stress.[5b,17-20] In the present case an attempt has been made to diminish the incidence of this error by two means: By observing the resting pulse and by training the observers to the process of pulse observation by frequent repetition. Since effective training requires from half a dozen to approximately three hundred repetitions,[21] it may be assumed that this process would be completed in from one to thirty days' time. Because each set of observations extended from a minimum of several months to a maximum of several years, emotional factors which affect one set of observations more than another would not be expected. There is no internal evidence to show that the process of training has not been successful.

The internal evidence may be analyzed as follows: The approach to training would be increasingly effective with time so that later observations should tend to be more reliable than earlier ones. Hence the observations taken before treatment might be somewhat less reliable than those taken after treatment, since much practice would have intervened. This error, if it exists, would manifest itself by a decrease in pulse reading with time. Since the objective of the treatment is to reduce pulse readings, the two phenomena might prove indistinguishable. In the case of the high readings, 100 per cent did show a decrease after treatment. In the case of the low readings, on the other hand, forty-seven patients showed a decrease, thirty-two patients showed no change and twenty-two patients showed an increase. Thus in 53 per cent of the cases there was either no change or an increase in the basal rate so that in these patients error cannot be

charged to diminishing excitement due to adaptation, even in the high values which did decrease with time.

Benedict and Carpenter,[22] who had patients count their own pulses while simultaneously recording them, came to the conclusion that the count registered by the subject is apt to be somewhat *lower* than that obtained mechanically. Their data show the difference to be two beats per minute, on the average. If one were to apply this as a correction, it would not change the statistical significance of Coca's observations but would diminish both upper and lower limits by two beats, leaving the ranges unchanged.

TABLE IV. EXTREME VARIATIONS OF HEART RATE ESTIMATES WITH CHANGE IN COUNTING INTERVAL ON ELECTROCARDIOGRAMS

Subject	Counted Rate	Estimated Heart Rates	
	60 Sec. Intervals	3 Beat Intervals	6 Sec. Intervals
A	73 Min.	67	70
	Max.	80	78
A	73 Min.	69	70
	Max.	83	80
A	67 Min.	64	66
	Max.	71	70
A	64 Min.	62	62
	Max.	72	69
B	77 Min.	66	70
	Max.	89	82
C	57 Min.	56	54
	Max.	64	60
Extreme variations from 60 second count	Min.	−11	−7
	Max.	+12	+7

2. *Duration of Observations.*—It may be argued that more reliable data than Coca's could be secured by some electronic means. Even in this case, however, the duration of the counting interval used for individual observations is of critical importance because of the high incidence of arrythmias.[23] Table IV shows the results of the analysis of electrocardiograms of three persons chosen at random from subjects in our laboratory. In this analysis heart rates counted for sixty seconds are compared with those estimated from shorter intervals of time on the cardiograms. Intervals of six seconds and three beats were chosen because of their frequent use in practice.

Inspection of the table will show that the largest variations are positive from the mean and that the variations are smaller with lower counts. Of course, so small a sampling cannot be regarded as representative.[23] The data do indicate, however, that the error of selecting too short a time interval for a mechanical counting may be gross.

With a variety of observers such as Coca used, the degree of attention to details of an indicated procedure may vary. In the present case, the observers were presumably instructed to count their pulses for one minute. That this instruction was not obeyed implicitly is evident from the data.

Statistical indications are that, of the 101 complete sets of observations, seventy-two persons counted for no more than half a minute and that seven of these probably followed the frequently used technique of counting for only fifteen seconds. Even the shortest indicated counting intervals are longer than many recorded from electrocardiograms and, since this interval is of such critical importance, Coca's observations may be more reliable than many electrically recorded observations. In future studies, however, strict adherence to the practice of using an interval of at least one minute should diminish the standard deviations of the observations, whether obtained by palpation or by mechanical means.

3. *Number Bias.*—A bias for recording certain numbers is not uncommon and is a source of error in precise measurements among most observers not especially trained to eliminate it.[24-26] The present group of observations contains more even numbers than it should as well as more numbers divisible by four than would be expected. Both of these findings are best explained on the basis of unconscious number bias. In addition, a special bias for the number 100 is indicated. It should be noted that a similar bias can occur in the manual transfer of measurements mechanically recorded by an instrument such as an electrocardiograph. Because of the rigorous training required to eliminate number bias, it is dubious that future sets of observations will be free from this error whether they are secured by palpation or by instruments unless a digital recorder is used.

DISCUSSION

The data of Coca may be used to formulate an approach to future studies of the maximum deviations to be expected in the behavior of "normal" human heart rates. "Normal" persons may be defined as those free from evident disease and free from the influence of pulse-accelerating foods, drugs or inhalants at the time of pulse counting. The values obtained after Coca's avoidance treatment appear to conform to these conditions. From the daily lows after treatment we found the average low reading of the 104 cases to be sixty-two beats per minute. From the standard deviation of the group the lowest expected reading was calculated as forty-nine beats per minute. The latter figure differs from that of Coca who states, "Normal rates as low as thirty-eight . . . have been observed."[1f] If we accept the criterion that deviations from the average of more than twice the standard deviation are suspect and warrant the search for an assignable cause, it follows that lows below forty-nine are not "normal" even though not necessarily pathological. Coca stated[1g] that these are values from highly trained athletes, so that the cause of their departure from population norms is probably their athletic training.[27]

The analysis indicates that a daily low above 75 would not be "normal" and that the maximum reading of a "resting" pulse should not be higher than 89 if the minimum is 75. Still lower values for the maximum are

to be expected if the low readings are less than 75. This conclusion differs slightly from that of Coca, who states, "Normal rates . . . as high as 84 (but no higher) have been observed."[1f,h] Table II shows that in about 25 per cent of all cases with daily minima above 70, high readings in the range from 85 to 89 may be "normal."

Coca states further, "normal ranges varying between 2 and 16" have been observed.[1f] Table II shows that the minimum "normal" daily range to be expected on rare occasions is one. However, this is beyond the precision of the measurements. This could be regarded as "normal" only with a person whose minimum was as high as 75. In Coca's table only one daily range as small as 2 is given. This is from 60 to 62. Statistically, this small excursion must be regarded as outside the normal range, since the minimum daily range to be expected with a low of 60 is 4. The pulse of the person with a low of 50 might have an excursion as large as 20 without exceeding the normal limit, while for a person with a low of 75, a daily range greater than 14 would not be "normal" and one of 16 would be too great.

Our figures are subject to revision as more data are gathered by more refined methods. In spite of differences in detail, however, they confirm Coca's underlying concept of the "normal" pulse, which emphasizes these points: (1) To attain full significance, readings must be taken systematically over an extended period of time and with a full record of proximity of meals, individual foods taken and the presence or absence of other significant chemical substances in the environment; (2) High readings are markedly affected by inhalants and by specific substances in the diet; (3) To secure a reasonable picture of the "normal" human pulse, it is necessary to control the diet by elimination of pulse-accelerating foods and the environment by the elimination of pulse-accelerating inhalants.

The fact that the "normal" daily range of the pulse is variable from individual to individual, even though it follows a general pattern, is of greatest importance in attempts to utilize pulse accelerations as an assay method or as a diagnostic technique. Table II shows that accelerations as small as three or four beats per minute might be indicative of a reaction in some individuals while a change as large as twenty beats might occasionally not be indicative of a reaction. The necessity for observations continued over a period long enough to determine the individual daily range is emphasized by this analysis. The assignment of a single range to all cases is an error which has been recorded in the literature in attempts at diagnosis.[11,28]

CONCLUSIONS

Our analysis of Coca's data permits the following additional conclusions to be drawn concerning the group of subjects on which his observations were made: (1) All four sets of data, minimum and maximum pulse rates, before and after treatment, fit normal distribution curves satisfactorily, indicating the absence of systematic bias in the selection of data.

(2) Avoidance of pulse accelerating substances significantly lowered daily maximum pulse readings. (3) As a rule, persons with low daily minimum pulse readings will have low daily maxima and *vice versa*. (4) The range between daily minimum and maximum pulse rates decreases as the value of the minimum increases. (5) Table II provides a means for the estimation of the normal daily range of the pulse rate of an individual if the daily minimum is established, thus supplying the clinician with a criterion for the better evaluation of a daily pulse curve in cases in which the diagnosis is difficult. (6) Daily minima below 49 should not be considered "normal." (7) Daily maxima above 85 are not "normal" except in the special cases in which the minima are above 70. (8) Daily minima above 76 are not "normal." (9) Examination of the low pulse values indicates that disturbances due to emotional excitement of the observers were probably not a critical factor in the observations. (10) The standard deviation of the observations could be diminished if the minimum counting intervals were consistently raised to one minute. (11) Evidence exists that Coca's observers were affected by a bias for even numbers, especially those divisible by four, and by a special bias for the number 100. (12) The number bias can be essentially eliminated in comparing groups of observations statistically, even though it does increase the standard deviations of the averages. (13) By indicating that statistically significant changes take place on dietary control, this study provides a justification for the further study of the pulse rate as a means of bio-assay in food-induced reactions that do not respond to skin testing or to immunological assay procedures.

It seems probable that the general technique proposed by Coca of reading the pulse systematically throughout the day and controlling the high excursions by means of dietary and environmental control is a valid one for the study of the "normal" human heart. The deficiencies of this study are mainly technical. With better counting techniques, and particularly with counting intervals no shorter than one minute, it should be possible to reduce the standard deviation of the observations. These improvements would alter the numerical details of the results and narrow the limits to be regarded as "normal." In future studies on the "normal" human pulse, the refinements in technique suggested by these studies should be taken into account.

ACKNOWLEDGMENT

The authors also wish to acknowledge the assistance of Professor A. J. Duncan in the statistical portions of the manuscript.

REFERENCES

1. Coca, A. F.: Familial Nonreaginic Food-Allergy. 3rd ed. Springfield, Ill.: Charles C Thomas, 1953. (a) p. 192; (b) p. 190-191; (c) p. 45, 65, 116 117; (d) p. 50; (e) p. 194; (f) p. 20; (g) p. 194; (h) p. 15.
2. Floyer, Sir John: The Physician's Pulse-Watch. Smith and Walford, London, 1707. (a) p. 70, 83, 84, 156; (b) p. 40, 81, 83; (c) p. 83, 156.

3. Lichtenfels, R. and Froelich, R.: "Beobachtungen über die Gesetze des Ganges der Pulsfrequenz und Körperwärme in den normalen Zustanden." Denkschr Wien Akad Wiss (math.-naturwiss. Klasse) 3:121, 1852.
4. Bleuler, E. and Lehmann, K. B.: "Ueber einige beobachtete, wichtige Einflüsse auf die Pulszahl des gesunden Menschen. Arch Hyg Bakt 3:215, 1885.
5. Boas, E. P. and Goldschmidt, E. F.: The Heart Rate. Springfield, Ill.: Charles C Thomas, 1932. (a) p. 95; (b) p. 100-102; (c) p. 23.
6. Coca, A. F.: The normal adult human pulse-rate. Ann Allergy 1:212, 1943.
7. Meyer, M. G.: Non-reaginic allergy. Ann Allergy 6:417, 1948.
8. Pollack, H.: Some Aspects of Food Allergy. 1st Internat Congress of Allergy. Zurich, 1951. p. 920. Ed. by A. S. Grunbach. Basle and New York: S. Karger, 1952.
9. Storck, H.: Die Bedeutung der Pulskontrolle nach Coca für die Allergiediagnose. *ibid* p. 658.
10. Massion, J.: L'Allergie Digestive Chronique D'Origine Alimentaire. Arch des Maladies de L'Appareil Digestif, 45:626, 1956.
11. Hafter, Ernst: Procede Diagnostique dans les Allergies Digestives. *ibid* p. 636.
12. Sanchez-Cuenca, B.: Problemas Actuales de Alergologia Clinica. p. 183. Editorial Saturnino Calleja, S. A., Madrid, 1954.
13. Fisher, R. A.: Statistical Methods for Research Workers. 13th ed. Edinburgh: Oliver and Boyd, 1958.
14. Zuntz, L.: Untersuchen über den Einfluss der Ovarien auf den Stoffwechsel. Arch Gynaek 78:130, 1906.
15. Harris, J. A. and Benedict, F. G.: A Biometric Study of Basal Metabolism in Man. Carnegie Inst Pub 279, Washington, 1919.
16. Bowerman, W. G. and Brett, J. H.: Pulse rates. Quart Rev Biol 16:90, 1941.
17. Menta, P.: Die Wirkung akustischer Sinnesreize auf Puls und Athmung. Phil Stud (Wundt) 11:61, 1895.
18. Billings, M. L. and Shepard, J. F.: The change of heart rate with attention. Psychol Rev 17:217, 1910.
19. Rihl, J.: Die Frequenz des Herzschlages. Hdb Norm und Path Physiol 7, pt. 1, p. 449 and 504, 1926.
20. Graybiel, A., McFarland, R. A., Gates, D. C. and Webster, F. A.: Analysis of the electrocardiograms obtained from 1000 young healthy aviators. Amer Heart J 27:524, 1944.
21. Pavlov, I. P.: Conditioned Reflexes. Trans. by G. V. Anrep. p. 27. London: Oxford Univ. Press, 1927.
22. Benedict, F. G. and Carpenter, T. M.: The Metabolism and Energy Transformations of Healthy Man during Rest. Carnegie Institute of Washington, Publ No. 126, 1910, p. 134.
23. Glynes, M. E.: Circulatory System: Respiratory Heart Rate Reflex (RHR) in Man: Mathematical Law. *In* O. Glasser, Medical Physics, Vol. 3, pp. 184-193. Chicago, Ill.: The Year Book Publishers, Inc., 1960.
24. Albrecht, S.: Personality in the Estimation of Tenths. Astronomical J (13) No 781, 33:103, 1920.
25. Gysel, H.: Unbewusste individuelle Schätzungs-Anomalien beim Wägen und ihre Auswirkungen auf die Genauigkeit von Mikro-Analysen 266-282. Mikrochemica Acta, 1953.
26. Corwin, A. H.: Weighing. *In* A. Weissberger, Physical Methods of Organic Chemistry, 3rd ed. Vol. I, part I, pp. 99-101. New York, N. Y.: Interscience Publishers, Inc., 1959.
27. White, P. D.: Bradycardia in athletes (below rate of 40), especially in long distance runners. JAMA 120:642, 1942.
28. Rinkel, H. J., Randolph, T. G. and Zeller, M.: Food Allergy, p. 169. Springfield, Ill.: Charles C Thomas, 1951.

34th and Charles Streets (Dr. Corwin)

COMPARATIVE EFFECTIVENESS OF BETAMETHASONE AND PREDNISONE IN CHRONIC BRONCHIAL ASTHMA

DONALD L. UNGER, M.D.
Chicago, Illinois

RENE BARTOLOMEI, M.D.
Ponce, Puerto Rico

THE EFFECTIVENESS of any new steroid is usually based on animal and laboratory studies, but we believe that many asthmatic patients can give an even more accurate evaluation. Some have been on almost constant dosages of prednisone for many months or years, and the slightest lessening in dosage results in prompt symptomatology. They are ideal standards by which the relative potency of any new steroid may be determined.

Betamethasone* (9 alpha-fluoro 16 betamethyl prednisolone) is a new steroid which has shown considerable effectiveness in allergic diseases.[1-4] Animal studies[5] indicate that 0.6 mgm is equivalent to 25 mgms of cortisone, 5 mgms of prednisone, 4 mgms of triamcinolone and corresponding dosages of the other steroids. The purpose of this study was to test the accuracy of these observations in our human "steroid meters," as well as to determine the effectiveness of betamethasone in chronic bronchial asthma.

METHOD

A group of thirty-six asthmatic patients who had been taking almost constant amounts of prednisone for three months or longer, substituted 0.6 mgm tablets of betamethasone for their 5 mgm tablets of prednisone. The group consisted of seventeen men and nineteen women with ages ranging from eleven to seventy-one (average age 50.4). They had been taking 5 to 15 mgms of prednisone a day (average 10.3 mgms) for from three months to six years (average 20.4 months). Two to four weeks after the substitution of the betamethasone for prednisone, they were asked which they found more potent, and what side effects, if any, had occurred.

RESULTS

Twenty-seven of the asthmatic patients found the 0.6 mgm tablets of betamethasone more potent than the 5 mgm tablets of prednisone. The other nine found no significant difference between the two. Not one patient said that the prednisone was stronger, although two stopped taking the betamethasone because of side effects. One developed epigastric pains which may have been related to an old peptic ulcer; the pains disappeared

Dr. Unger is Clinical Assistant in Medicine (Allergy), Stritch School of Medicine (Loyola); Adjunct Physician, Michael Reese Hospital, Chicago, Illinois.

*Supplied as Celestone by the Schering Corporation, Bloomfield, New Jersey.

when he switched back to prednisone. The other said that the betamethasone made her nervous and constipated. Several patients developed an enormous appetite while taking betamethasone. Perhaps the most significant finding was that many patients were able to remain symptom free on half as many tablets of betamethasone as of the 5 mgm prednisone.

SUMMARY AND CONCLUSIONS

Thirty-six asthmatic patients on long term corticosteroid therapy substituted 0.6 mgm tablets of betamethasone for their 5 mgm tablets of prednisone. Twenty-seven found the betamethasone more potent, and the other nine noted no difference between the two drugs. Two patients stopped taking betamethasone because of side effects. It appears that 0.6 mgms of betamethasone is stronger than 5 mgms of prednisone in chronic asthmatics. Perhaps a smaller dosage tablet would be advisable.

BIBLIOGRAPHY

1. Bukantz, S. C.: Observations on the use of betamethasone in the intractable asthmatic child. Paper presented at First Symposium on the Clinical Application of Betamethasone: A New Corticosteroid, New York City, May 8, 1961.
2. Hampton, S. F.: Betamethasone—a new steroid in allergy: a preliminary report. Ibid.
3. Schwartz, E.: Clinical evaluation of betamethasone in chronic intractable bronchial asthma. Ibid.
4. Bedell, H.: A new systemic steroid in the treatment of allergies in office practice. Ibid.
5. Cecil, R. L.: Continued progress in corticosteroids. Ibid.

185 North Wabash Avenue

THE VALUE OF A HYPOTHESIS

In order to ascertain the value of a hypothesis, we launch an experiment and, as we said before, we repeat it many times. This may be enough if the experiment was well conceived and if its results are clear and precise. But even in this case, it would be a mistake to disregard the mass or quantity factor. The conclusion that we have reached acquires undoubtedly much more value and is accepted much more readily and favorably if we arrive at it in several different ways. Hence, it seems to be advantageous at least, to answer the hypothetical question through several series of experiments conceived on different plans—when our imagination permits us the treat of such a scientific luxury. It is a luxury, of course, but it is quite good to be able to lavish occasionally, even in science.—Maurice Arthus' *Philosophy of Scientific Investigation*, HENRY E. SIGERIST, Editor, The Johns Hopkins Press, Baltimore, Md., 1943.

Basic Briefs

MISCELLANEOUS INHALANTS

HOMER E. PRINCE, M.D., F.A.C.A.
Crockett, Texas

THE TERM *miscellaneous* is ordinarily applied to those inhalant allergens not included among the pollens, mold-fungi, or insects. By strict definition, the list could be almost endless, but in common usage this grouping excludes those allergens ordinarily regarded as foods, but which occasionally cause allergic symptoms by inhalation, as well as substances of known chemical composition. The most common allergens of this somewhat heterogeneous classification are household or environmental dusts, animal danders, hairs or scales, insecticides of vegetable origin, some cosmetic ingredients, and seeds.

House Dust.—House dust is by far the most important of the miscellaneous inhalants. Ordinarily house dust is a relatively "weak" allergen, but its significance reflects its widespread distribution, frequent high concentration, and a common sensitizing property apparently not entirely related to geographic or climatic factors.

Most writers agree that decomposition products of cellulose, especially cotton lint, constitute a large portion of the house dust allergen, and some believe these substances determine the "specificity" of house dust. Also recognized frequently in house dust have been human and animal hairs and epithelial scales, animal danders, feather particles, rodent feces, insect scales and excreta, glue, tobacco, plant fibers, seed particles and pollen. Proof of additional specific allergenicity of any of these substances, however, has ordinarily not been conclusive. Bacteria and fungi almost always are present in house dust, and the latter have at times been thought to determine specific differences in allergenicity; both may be important in further degradation of all the other constituents.

The house dust "season" occurs for the most part in the winter months, from early fall to late spring in northern latitudes, in mid-winter only in the South. This seasonal trend is obviously a reflection of decreased ventilation, increased use of dust-forming articles such as bed covers and drapes, and lowered indoor humidity in heated homes to promote dissemination in the winter. On the other hand, house dust is often a perennial allergen for highly sensitive persons, chambermaids, janitors, renovators, or others who

Presented at the Seventeenth Annual Graduate Instructional Course in Allergy on March 13, 1961 at the Statler-Hilton Hotel, Dallas, Texas.

have unusual exposure. Paradoxically, house dust is sometimes a typical summer allergen when it is encountered in summer homes or camp houses which have been unoccupied during other seasons of the year.

House dust may be the only significant inhalant allergen, but in many patients it is a complicating factor for other sensitizations; in either capacity, it must be considered in the course of clinical treatment. As with other allergens, avoidance would be the best treatment, but because of the universal distribution of house dust, complete avoidance is virtually impossible. However, measures directed to reducing dust contact in the home environment may be the only therapy necessary in mild degrees of clinical sensitivity. Such dust control programs are of great importance prophylactically to minimize further or prevent future sensitivity. The chances for success from injection treatment, which is usually necessary in the clinical management of dust-sensitive patients, are greatly increased if environmental dust control can be accomplished to a fair degree.

Practical instruction in house dust control measures must emphasize the fact that lint-producing articles are the main source of dust. Bedding materials including blankets, quilts, and mattresses containing cotton, feathers, wool and kapok must be replaced with articles made from synthetic fibers or sponge rubber. When mattress or pillow replacement is impractical, complete enclosure in plastic envelopes is quite satisfactory; such enclosure is necessary if box bedsprings are to be retained. Furniture upholstered with natural fibers must be treated similarly. Heavy wool and cotton draperies should be replaced with synthetic fabrics; light cotton drapes may be permitted, if they are laundered every three weeks. Rugs and rug pads of natural fibers should be eliminated or kept to a minimum, especially in the bedroom; they must be thoroughly vacuum-cleaned three times weekly; synthetic carpeting and rubber pads are preferable. Storage facilities in or opening into the bedroom should be emptied of old clothing and bedding, and thoroughly cleaned; the clothing worn frequently, however, may be kept in dresser drawers or bedroom closets.

Thorough vacuum cleaning of the entire house to include upholstered furniture must be carried out three times weekly; at least once a month, walls, ceilings and lighting fixtures should be vacuum-cleaned or wiped with a lightly oiled rag. Dust sealing chemicals may be sprayed periodically on dust-producing fabrics, but in my experience this is a compromise measure to be avoided if possible.

Feathers.—New feathers are seldom allergenic either by skin test or actual exposure. The frequent allergenicity of feathers reported in the earlier literature may have been based on tests with extracts of *old* feathers, which are very allergenic. There is evidence that patients sensitive to house dust are frequently sensitive to old feathers; indeed, the parallellism suggests that old feathers in the heterogeneous mixture known as house dust may add a significant allergenic fraction. On the other hand, it is also

possible that the same decomposing factors operative on cellulose and other house dust constituents exert a similar activity on feathers. Feathers found in the home in upholstery, pillows, mattresses and comforters are likely to be old, and, therefore, highly allergenic. Feathers must be replaced, or covered with impervious encasings.

Occupational or Special Environmental Dusts.—Hay, grain, and other livestock feeds may impart specific allergenicity to dust in barns, warehouses, and feed stores. Grain milling and processing plants often liberate sufficient dust to contaminate large areas of the surrounding countryside. Bakeries, food-processing plants, binderies, and textile mills produce their peculiar dusts with specificity determined largely by one or more crude products employed in their operation. Dusts from many of these sources frequently have a high mold content, and some also are contaminated by mites and weevils to further provide complex reaction patterns.

Animal Danders and Hairs.—Animal hairs and danders usually originate from such sources as household pets, agricultural livestock, or hide and fur processing plants. Frequently, however, animal contact is not obvious, and can only be discovered after positive skin tests demand exhaustive investigation. Typical examples are the old-style rug pads, and sometimes upholstered furniture, which may have been manufactured from horse or cow hair. An unusual animal contact is often not suspected—a pet guinea pig surreptitiously kept in her bedroom by one of my problem patients—and, therefore, will not be considered in routine diagnostic tests.

Animal danders and hairs are among the most allergenic of all inhalant substances, and symptoms frequently follow minute contact. Clinically significant quantities may remain in contaminated environments for periods of several months, even after frequent thorough cleaning; this is especially true of cat hair. Avoidance of animal danders is the preferred treatment, but cautious injection treatment occasionally is necessary.

Insecticides.—Pyrethrum and derris root are vegetable substances formerly used extensively both in powder and extract form in insecticide mixtures. With the advent of DDT and other chemical insecticides during the past few years, pyrethrum and derris root are now employed only occasionally in commercial insecticide mixtures, usually in combination with one or more of the complex chemical agents. Most of the insecticide chemicals are toxic, and may produce respiratory symptoms on an irritative basis; they are frequent causes of contact dermatitis. Avoidance is the only treatment of respiratory irritation from chemical ingredients of insecticide mixtures, but hyposensitization may be tried if allergenic activity of derris root or pyrethrum is involved.

Cosmetics.—Powdered orris root was formerly a commonly encountered inhalant allergen in many cosmetics, especially face and body powder. For several years, however, competition by hypo-allergenic cosmetics, advertised to contain no orris root, has forced most American cosmetic manufacturers to discontinue the use of this potent allergen. On the other hand, orris root is still employed in some cosmetics of foreign manufacture, and occasionally in certain domestic products. Treatment of highly sensitive persons is best accomplished by avoidance; occasionally hyposensitizing injections may be necessary.

The odors of essential oils in perfumes may be aggravating factors in respiratory allergic diseases. The oils are also occasional causes of contact dermatitis.

Seeds and Herbs.—Seed particles are extremely potent inhalant allergens, capable of producing violent symptoms from minimal contact. Flaxseed is sometimes contained in commercial poultry feeds and flaxseed meal is occasionally still used as a poultice. Cottonseed is perhaps more frequently encountered than is commonly suspected. It is a common cattle feed in the South, and may be an ingredient in some commercial lawn fertilizers. Cottonseed particles in "cotton linters," an inexpensive upholstery and bedding material, has been thought to contribute to the allergenicity of house dust. Almost any other seed species, and rarely dried herbs, may become inhalant allergens in special environments, for example, in the pharmaceutical manufacturing industry.

P.O. Box 979

THE MILIEU INTERIEUR

The living organism does not really exist in the milieu extérieur (the atmosphere, if it breathes; salt or fresh water, if that is its element), but in the liquid milieu intérieur formed by the circulating organic liquid which surrounds and bathes all the tissue elements; this is the lymph or plasma, the liquid part of the blood which, in the higher animals, is diffused through the tissues and forms the ensemble of the intercellular liquids and is the basis of all local nutrition and the common factor of all elementary exchanges.

The stability of the milieu intérieur is the primary condition for freedom and independence of existence; the mechanism which allows of this is that which ensures in the milieu intérieur the maintenance of all the conditions necessary to the life of the elements.—CLAUDE BERNARD.

Progress in Allergy

MICROBIAL ALLERGY

A Critical Review—1950-May 1960

HERMANN BLATT, M.D., F.A.C.A.
Cincinnati, Ohio

PART II

COMPLEXITY OF ALLERGIC REACTIONS

Spougitch[125] studied systematically the allergic conditions in workers of various factories and inhabitants of different regions of Yugoslavia for evaluating the complexity of the mechanism of allergic reactions. He found that asthma and other allergic manifestations in individual cases and in various regions, are the results of several factors, the most important being sensitization, formation of shock tissue, hypersensitivity of the factors, and inherited predisposition. Each of these factors is dependent upon many special conditions; they do not all take part in the anaphylactic reaction. They do lead to allergic reactions, which are more valuable and more numerous than the anaphylactic reaction.

INTERRELATIONSHIP OF ALLERGY, INFECTION, AND THE PSYCHE

"Both infectious states and psychic factors participate in the production of disease" (Prigal[126,127]). According to Prigal, infection, allergy, and the psyche play an interlocking role in the problem of allergic disease. Taking all three factors into consideration, "we may be able to indicate a unified approach which can elucidate the relationships among all three aspects." Regardless of all causes, Prigal believes we may consider all disease as a disturbance of homeostasis. Such a concept implies a constant interplay of opposing forces. When balanced, they permit a state of well-being, but when unbalanced by one force or set of forces, a state of disease is produced. The interplay of these diverse factors is a highly complex problem indeed, "since each of the factors comprising it is in itself complex." Each of these factors is not only capable of producing disease, but each itself can initiate vicious cycles or chain-type reactions. Since they are a form of stress, their interrelationship might be mediated by the pituitary-adrenocortical axis.

The importance of the role of infection in allergy is becoming more and more recognized. This is particularly true for respiratory and skin allergies. Prigal is of the opinion, however, that "aside from the tuberculin reaction, the delayed type of bacterial allergy is relatively infrequently encountered, despite the fact that allergic diseases are so commonly associated with active chronic infection." The acute form of bacterial allergy (anaphylaxis) is a rare clinical phenomenon. Skin testing with bacterial antigens has only led to confusion in clinical evaluation, because immediate and delayed reactions are obtained and mostly cannot be correlated with clinical findings or cultures of the present illness. "The clinician is there-

fore limited to the deliberate production of symptoms by injections of bacterial antigens as the only reliable, albeit limited, means of diagnosing clinical bacterial allergy in the asthmatic patient."

Proven cases of bacterial allergy are rare in clinical practice. This may be due to our poor diagnostic techniques, but Prigal is of the opinion that more likely, "the allergist will have to cling less to this cherished concept of bacterial sensitization and consider more the other roles that infection can play in clinical allergy." He believes that because of the many clinical entities demonstrating a variety of interrelationship between infection and allergy, "the necessity of seeking a single explanation, such as bacterial allergy, for all of them seems obviated."

There is experimental evidence for other relationships between allergy and infection. For example, staphylococcal toxin may induce a type of autosensitivity[128] and other infections or their agents may enhance sensitivity.[129,130] It has also been stated that pertussis vaccine enhances the induction of experimental allergy.[131] "Since pertussis prophylaxis in infancy is almost universal in this country, one wonders what role, if any, it plays in the induction of allergy."[132]

Infection may also simulate the allergic state pharmacologically. Dworetsky and co-workers[71] induced anaphylactoid reactions in guinea pig ileum with a pathogenic strain of staphylococcus. These reactions were indistinguishable from typical allergic muscle contractions induced on an antigen-antibody basis. Prigal does not consider this a truly allergic response, but an allergy-like reaction caused solely by the pharmacologic properties of the extract. This finding might explain some of the unexplainably severe asthma cases associated with infection. He cites his own investigations[133] where he found hemolytic and coagulase-positive streptococci more frequently in asthmatic patients and their families than in nonasthmatic control families. Such organisms should not be overlooked just because they are generally nonpathogenic. Through additional factors, the host's resistance can be changed and such organisms produce active infection and disease. Perhaps, he comments, "pre-existing allergy may provide one of those necessary conditions for maintaining infection and for converting latent infection to the active state."

Prigal raises the question whether allergy modifies infections. He cites his experimental studies together with Dubos,[134] whereby they produced a systemic type of sensitization (nonfatal anaphylaxis in the mouse), and made the host exceptionally vulnerable to infection with a standard strain of staphylococcus.

Prigal believes there is sufficient evidence to suggest a "multidirectional relationship between the psyche and allergy." Because most allergists are unfamiliar with Freudian concepts, the Freudian approach to this problem is unacceptable to them. But there are no obvious incompatibilities between the basic concepts of psychiatry and allergy. Experimental injury in the tuberal brain areas can prevent or reduce anaphylaxis. This may be mediated through interference of antibody production.[135]

DIAGNOSIS IN MICROBIAL ALLERGY

There is much confusion in the literature as to the value of skin testing with bacterial antigens. The results of skin testing to bacteria vary greatly in the hands of different investigators. The problem is made more difficult, because both immediate and delayed types of reactions can be obtained from antigens of the same source. Hansel,[136] in his book on allergy, points out

the need for diagnostic procedures other than skin tests to establish a relationship between bacteria and syndromes of clinical allergy. Forman[137,138] reports patients with the immediate type of reaction to *Staphylococcus albus, Staph. aureus, Streptococcus viridans, St. hemolyticus, Str. pneumococcus, B. coli* and Friedlaender's Bacillus. In elderly patients, however, he frequently gets no skin reactions and uses the Blatt-Nantz test for diagnosing such cases. Herxheimer[139] found skin testing of limited value. Walzer[140] finds that delayed reactions vary too much in mechanism and significance to be reliable for diagnostic purposes. I, myself, use the Blatt-Nantz test[141,142] for diagnosing and treating patients suspected of bacterial allergies.

Many clinicians do not rely on bacterial skin tests because frequently they obtain positive skin reactions in healthy individuals having no clinical symptoms of bacterial allergies.

This, in my opinion, is not as valid an argument against the efficacy of bacterial skin tests as some other factors. After all, skin-test reactions in atopic allergies also require clinical judgment and experience for a proper interpretation. As early as 1922, Peshkin and Rost[143] tested 502 apparently nonallergic children to foods and inhalants, and had 10 per cent positive reactions.

It is interesting to speculate whether positive bacterial skin tests in apparently healthy individuals may be a sign of increased suspectibility to infection, or increased resistance. Although immunologists and allergists interested themselves very much in this problem in the earlier part of this century, it seems that little has been written lately on this subject.

Probably one of the main reasons why opinions as to the value of bacterial skin tests are so varied, is because of the difficulty in making good bacterial antigens. Bacteria have a complex structure. We have not as yet identified with certainty the factors that make up a specific antigen of a bacterium. The cytoplasm of the staphylococcus, for example, is composed of nucleoproteins, polysaccharides, metabolic products that may be necessary to serve as haptens in sensitization, as well as toxins which may or may not play a contributory role in the sensitization process.

Swineford[144] made 3,860 intracutaneous skin tests with thirty-four crude polysaccharides and nucleoprotein fractions of fourteen different bacteria. Although he had many immediate and delayed reactions, no causal relationship between the diseases and positive tests was noted. Behounkova and his group[145] believe that bacteria form just a small part of the total "antigenic spectrum of microbes" and that the secretory products of the bacteria, the exotoxins, and the exoferments are more important. They use the supernatant of bacterial cultures, cultivated in solid culture media on cellophane. This supernatant substance contains a small but sufficient number of microbes as well as all their soluble non-protein products. Several hundred skin tests were performed with this material. The results obtained convinced these investigators that the "microbial antigen complex obtained by means of the cellophane cultivation method is of greater importance for the allergization of the organism than the bacteria or the abacterial secretion products themselves."

Various diagnostic procedures have been devised in recent years for confirming the diagnosis of bacterial allergy. Many Europeans have found Mulder's[146,147] method highly effective for distinguishing cases that are noninfected and those with bacterial allergy. He described in 1937 a technique of washing the secretions and eliminating normal oral and pharyngeal bacteria and cells. Van Ufford found Mulder's method satis-

factory for making certain that one is not growing cultures of normal tracheal flora. He also accomplishes this by comparing tracheal smear cultures with sputum cultures of the patient. Bergman and his associates[148] described a method whereby bronchial infection can be identified through culture of bronchial secretions collected by sterile suction cups, that is, catheterization through a tracheal tube under anesthesia.

The use of nasal smears for differentiating between atopic and bacterial allergies or bacterial infections has become a common procedure in most allergists' offices. Hansel's[149] "Improved Method of Rapid Staining" has proved quite useful. In bacterial allergies, I rely on the Blatt-Nantz test and also treat with the same filtrates which gave positive reactions. This test is based on the fact that the white cells from cases of bacterial hypersensitivity are killed *in vitro* by contact with the products of the specific bacteria.

For our test, I now draw 12 ml of the patient's venous blood, divide it into three tubes, each containing 0.5 ml of a 2 per cent solution of sodium citrate and allow it to settle. The supernatant plasma is withdrawn and the underlying white cells are coagulated into a buffy coat with calcium Ringer's. The white cells can be lifted out of the tube, red cells clinging underneath are cleaned off and the buffy coat dropped into Ringer's solution to be freed. The coat is then shredded and suspended in a bottle containing 1.5 ml of sterile Gay's or Ringer's solution, placed in the incubator at 37.5° C for one hour. From time to time it is vigorously shaken.

For the actual testing, one drop of this white cell suspension, one drop of bovine thrombin containing 200 units per ml, and four drops of 1:1000 dilution of filtrate, are put in a sterilized well, covered and ringed with vaseline and incubated for seventeen hours at 37.5° C. The leukocytes are then examined under the microscope for cell damage.

In developing the test, we made careful time studies and found that seventeen hours was the optimum time in which to make the microscopic examination of the well.

Routinely, a carefully selected collection of 161 filtrates of different bacterial strains is employed. Additional ones are added if the history of the patient so indicates. Autogenous filtrates also are sometimes run. The same filtrates, which produced positive reactions four consecutive times, are then diluted with physiologic saline and used for desensitization.

The actual testing takes the time of two technicians for the greater part of four days. This does not cover the time consumed in preparing to make the test, cleaning up afterwards, and other incidentals. The tests, therefore, are a practical procedure only when the clinical findings and the history very strongly suggest a case of so-called "intrinsic allergy."

We also found that our test cannot be used for the diagnosis of atopic allergy. The leukocytes of patients with pure atopic hypersensitivity are unaffected by the specific atopic antigen to which the patient is allergic.

The study of nasal secretions for eosinophilia is practically standard procedure for allergists and otolaryngologists. William and Marion Bryan[150] recently discussed the role of mast cells in nasal secretions. They believe more interest should be shown for this aspect. In 340 cases of allergy that they studied, 194 smears showed an increased number of mast cells. Apparently, these authors do not believe that there is such a thing as bacterial allergy but they find mast cells important for differential diagnosing of the bacterial or second phase of the "acute rare bacterial rhinitis and the common chronic sinusitis of indefinite duration," from other forms of nasal allergy.

It is generally agreed that skin tests for fungus hypersensitivity as well as skin tests for certain ailments such as, for example, the tuberculin test, are reliable diagnostic procedures. The newer diagnostic aids described for detecting bacterial allergies represent a definite advancement in the field of microbial allergy. They are useful research tools, and practical aids for those who have the facilities for using them. The need remains for simpler procedures that can practically be carried out in every busy clinician's office. It is to be hoped that with the increased interest being shown in this field, the time will not be too distant when someone will devise such a method.

The real problem in the interpretation of the skin test to microbes is not the failure to obtain specifically positive tests, but the determination of their significance in relation to the patient's presenting hives, coryza, asthma, eczema, or migraine. As in all cases, a positive test may represent a previous episode in the past of the patient. It does establish that the patient is specifically hypersensitive to the group of germs under study. But the question presented is—what is the relation of this particular hypersensitivity to the presenting symptoms in the case at hand? Too often, this possibility is not pursued to its solution, but rather ignored entirely and not even tested. On the other hand, less frequently it is overemphasized without sufficient data.

VACCINE THERAPY

Although the use of bacterial vaccines and filtrates is still controversial, most physicians use them. The controversy, however, is over the manner of their action and not their value. Some are of the opinion that they represent only another form of nonspecific stimulation of the antibody mechanism, or possibly that they affect the enzymatic systems in some favorable way. Some physicians use them only as a last resort, while others use them routinely in all so-called "intrinsic cases." I feel that if proper criteria are used in the selection and administration of the vaccines or filtrates, their use is immunologically sound. With me they are more than useful, because the filtrates are the real crux of my treatment program.

At present, the literature seems to be about equally divided between the use of stock and of autogenous vaccines. The decision to use one or the other should, in my opinion, depend upon the individual case. We are not reproducing natural conditions in human organs with our present-day methods of growing bacteria, and obtaining material from so-called foci of infection does not necessarily mean that we have the basic antigens. It is too often forgotten that during the amnastic phase in many conditions, the antigenicity of the bacteria has changed, and the material we obtain is not responsible for the clinical picture. Considerable research is still needed before we have the proper answers. In my own experience, when I obtain positive findings with autogenous material using the Blatt-Nantz test, I will generally achieve desirable therapeutic results. When the test to the autogenous material is negative, however, a good stock filtrate or vaccine promises greater success. If the clinician lacks facilities for preparing a good autogenous vaccine, then he does better to use a well-prepared stock one.

Most of the literature written by allergists about vaccine therapy deals with the results of treating asthma. Frankland, Hughes, and Gorrill[151,152] found that regular injections of an autogenous bacterial vaccine produced no greater benefit to asthmatic patients than similar injections of carbol

saline. This contrasts with the experience of Colldahl[153] who had satisfactory results with both stock and autogenous vaccines. Hajos[154] believes that Frankland's studies can lead to wrong conclusions because he used a 0.5 phenol solution as a placebo. This has antihistaminic activity, and, according to Hajos, could produce transitional or even prolonged improvement. The late Urbach[155] favored autogenous vaccines, while Kaemmerer[156] reports good results giving vaccine therapy to asthmatics. Wilken-Jensen reported that 85 to 90 per cent of his asthmatic children became symptom-free following long-term therapy with a vaccine prepared by the Danish State Serum Institute. Hajos[157] is a staunch advocate of autogenous vaccines in asthmatic patients with a history of infection, although he believes that good results are dependent upon careful search for foci of infection, bacteriologic examination of the patient's sputum, and the nasal and pharyngeal secretions. In culturing the bacteria, he adds the patient's serum to the blood agar cultures after the bacteria have been killed very cautiously. He recommends this procedure because, in this manner, the bacteria against which the organism was protected are suppressed, while the disease-producing ones continue to grow. His vaccines from stool cultures are prepared in the same way. Vaccines manufactured by this process must be given in small doses, because violent reactions can occur. Hajos has also observed that asthmatic patients benefited by streptococcal and enterococcal vaccines made from the duodenal secretions of the patients. This has also been my experience. I have had several refractory cases which responded to vaccine therapy when organisms such as *Salivarius mitis* were cultured from the stools. It is important to bear in mind that occasionally organisms of the gastrointestinal tract can be a factor in asthma. Even the allergist too frequently forgets that nonvirulent organisms can be strong sensitizers, and many cultured organisms that may be insignificant to the pathologist can be an important factor in the allergic patient's symptoms. Because allergies are often caused by non-pathogenic organisms at sources that do not manifest themselves clinically, Hodek[158] cautions that material for autogenous vaccines should be obtained from every possible source. According to him, the bacterial material must be processed as soon as possible in order that no organisms die. Following Fleming's rule, Hodek uses only a few of the bacterial strains he obtains for injection therapy. The number of microorganisms is important, but there is no agreement on the number of doses. Hodek's article, to my knowledge, is one of the very few that discusses the number of organisms to select for treatment. Here, too, methods vary, as some clinicians use every organism they obtain, while others have their own theories of selection. This is another example of how much we have yet to learn.

According to Hodek, patients with specific lung processes or serious diseases of the parenchymatous organs should not receive autogenous vaccines. Contrary to the experience of this reviewer, Hodek reported that those receiving corticosteroids simultaneously, more frequently had reactions and sometimes tolerated vaccine therapy poorly. As an interesting incidental note, Hodek observed that some of his patients were less sensitive to dust after vaccine therapy.

In the study of Helander,[159] forty-four patients with "infective" bronchitis received autogenous vaccine, forty-three received an autogenous vaccine from asthmatic patients' expectorations, and 141 patients were given stock vaccines (Parke-Davis anti-catarrhal vaccine, the Swedish State Bacteriological Laboratories staphylococcus vaccine, and various other mixtures). No difference in the therapeutic effects was noted. Helander also conducted

a double-blind study of vaccine and placebo treatment. Here also, no difference between the therapeutic effects was found. Helander believes that "the effect of bacterial vaccine therapy in infective bronchial asthma is due to psychological factors." Since vaccine therapy is not entirely without risks; he warns to "be restrictive with it."

Van Ufford[160] also advocates the use of vaccine therapy in asthma, and applies certain criteria in the selection of patients for autogenous vaccines: (1) patients with bronchial asthma, subjected to continuous attacks of bronchitis; (2) patients with bronchial asthma, showing large numbers of focal infections and in whom there is apparently a relationship between the infections and the attacks of asthma; (3) patients with bronchial asthma liable to frequent attacks of dyspnea following colds, bronchitis, et cetera (this group often includes children); (4) patients with bronchial asthma who do not show any intervals free of symptoms between attacks, but continue to cough and expectorate; (5) patients with bronchial asthma showing markedly positive skin tests for one or several bacterial allergens, whereas no definite focus could be detected; (6) patients with emphysema and recurrent bronchitis. When stock vaccines are ineffective, Van Ufford frequently achieves results by making a new vaccine.

Newport[161] reports that, for the past thirteen years, he has been preparing autogenous bacterial antigens using the patients' blood as the entire culture medium. These antigens have been used principally in the treatment of chronic upper and lower respiratory infections apparent as a primary or secondary factor in the allergic patients he has treated. Chronic allergic and infectious rhinosinusitis, bronchitis, bronchial asthma, emphysema, and rheumatism have been manifested in these patients. Newport advocates the use of the patient's blood, as it is a convenient sterile medium, which is not, in the broad sense, a foreign substance to the allergic patient. Moreover, it satisfies the requirements of a culture medium which most nearly duplicates the body tissues of the patient. By the use of a technique involving the grinding up of the culture and blood medium *in toto* and the preparation of a Seitz filtrate, he has produced antigens which, he contends, are more complete since they may be presumed to contain both exotoxins and endotoxins. In over-dosage, these antigens have repeatedly been found capable of reproducing symptoms of respiratory congestion, asthma, and arthritis. And in at least 90 per cent of patients given guarded increases of dosage, according to their tolerance, the antigens have effectively afforded prolonged periods of complete relief. Besides these benefits, they also yield definite positive, delayed type, skin tests in relatively high dilutions. According to Newport, it would appear, from the reproduction of symptoms by bacterial antigens, which also show positive skin tests, that the existence of bacterial allergy in such patients is self-evident. He cautions, however, that the degree of reaction and the dilution at which it appears do not furnish a reliable index of the patient's tolerance of the antigens when used in treatment.

A controlled study was made of fifty patients previously refractory to all other treatments, who were considered to have a strong element of chronic infection contributing to, or being the probable sole cause of, chronic rhinosinusitis, bronchitis, and bronchial asthma. The rough microscopic analysis of samples of cultured materials from this study appeared to show the following:

1. The percentage of patients' cultures showed major growths of the following organisms: long-chain Streptococci with Alpha hemolytic property (66 per cent), *Hemophilus influenza* (40 per cent), *Diplococcus pneu-*

moniae (36 per cent), short-chain Streptococci (hemolytic) (30 per cent), staphylococci (6 per cent), *Klebsiella pneumoniae* (6 per cent), and *Neisseria catarrhalis* (6 per cent).

2. Predominant growths of organisms seemed to indicate selective quality of the patients' blood against which immunity may be presumed to have been relatively gained. The observation of this predominance of growth was seen only in long-chain streptococci (44 per cent), *Hemophilus influenza* (24 per cent), *Diplococcus pneumoniae* (14 per cent), and short-chain streptococci (18 per cent). Staphylococci, *Klebsiella pneumoniae,* and *Neisseria catarrhalis* never were predominant growths, while *Histoplasma capsulatum* (6 per cent) and *Aspergillus sp.* (4 per cent) were incidental findings in the cultures studied.

In each instance, the culture of those patients who experienced constitutional reactions to overdosages, with a marked flare-up of chronic rheumatic symptoms associated with their chronic respiratory infection, showed predominant growths of the short-chain Streptococci. In previous cultures made by Newport on arthritic patients (not included in this group) in which he used extracted teeth and throat cultures as source material, there were, almost invariably, predominant growths of short-chain Streptococci manifesting a high degree of hemolytic property in their growth upon the blood medium.

Sanchez-Cuenca,[162] Hebald,[163] Sherman,[164] and Henricksen[165] all report favorable results in treating asthmatic patients with vaccines. Sherman warns that these must be given very cautiously, since many patients are highly allergic to bacterial products.

In complicated asthmatic cases, where there is a yellowish sputum and bacterial allergy is probably involved, Morietti[166] uses a stock vaccine of the Delbet broth type. The initial dose is 0.05 ml. The injections are given three times a week in increased amounts until a dose of 1 ml is attained. He also uses stock vaccines.

Administering autogenous vaccines with asthmatic patients is sometimes a specific and other times a non-specific form of desensitization (Spuzic, et al[167]). Autogenous vaccines are also a stimulating treatment because of their action on chronic changes of the bronchial tubes. They decrease the effect of contributory and localizing factors. Despite the many favorable reports of treating asthma with vaccines or autovaccines, the beneficial effects are generally of a temporary nature lasting, at the most, two years. In view of this, Spuzic recommends repeating the injections, especially in autumn. Giving autovaccines exclusively in asthma is generally not enough; antibiotics, according to him, should also be given.

In our own experience, we have had excellent results by injecting filtrates; "follow-ups" showed a large percentage of patients did not have recurrences. However, the average treatment lasted twenty-nine and one-half months. Giving antibiotics concomitantly produced still better results and the average treatment was reduced to seven months. The dosages of antibiotics need not be as large as in cases of frank acute infection.[168,169]

Rose[170] uses autogenous vaccines and filtrates prepared from nose, throat, and sputum cultures in addition to stock bacterial filtrates based on the patient's skin-test reactions to them. He also used pooled vaccine isolated from persons in his local area who had chronic recurrent respiratory infections with and without associated allergies.

Hansel[136] concedes that good results are obtained with vaccines and filtrates, but he believes that this is due to a non-specific mechanism. This,

in his opinion, explains the excellent therapeutic results he obtains with staphylococcus toxoid.

Tabart[171] finds specific treatment in microbial allergies as unsatisfactory.

Jimenez Diaz[172] treats his patients with pooled polysaccharides of the bacteria.

Heise[173] believes that the long-chain streptococci are mostly responsible for bacterial allergies of the upper respiratory tract and reported a method for obtaining these and using them for treatment. With clinical improvement, the long-chain streptococci disappear from the smears.

Baird[174,175] uses for bacterial allergies "serobacterin," a sensitized vaccine. This vaccine contains no serum but has both bacterial antigen and antibody in contrast to most commercial preparations. He attributes his success to giving larger doses than those recommended by the manufacturer. He gives, three to seven days apart (depending on the dosage), subcutaneous doses of 0.2 cc, 0.4 cc, 0.8 cc, 1.2 cc, 1.8 cc, 2.5 cc. The 2.5 cc dose is usually repeated at intervals of one to three weeks. In a few intractable cases he gets good results by giving doses of 3 cc.

Storch[176] reports good results using Serobacterin, especially in dermatologic cases. His results with vaccine therapy had been unsatisfactory before using this product.

Pryomen is a highly refined bacterial product containing complex polysaccharides. Although originally intended as a readily controlled pyrogenic agent, it was discovered that constitutional reactions caused by Pyromen were beneficial in treating allergic conditions. The literature is very conflicting as to the efficacy of this form of treatment. Randolph and Rollins[177] wrote a very comprehensive report on its use in various allergic conditions. They found it helpful as an adjunct non-specific treatment in bacterial as well as other allergies. Failures, in their opinion, are due in many instances to not individualizing the doses in different subjects. Wittich, using Pyromen, treated fifty patients having respiratory allergies. Only twelve were benefited in his series.

In the twenties and early thirties of this century many American investigators interested themselves as to the value of oral bacterial vaccine therapy. I personally do not know one allergist in America who uses this method today. However, in Europe (especially Germany) interest is being revived in this field. One German preparation on the market (Paspat) contains a polyvalent antigen mixture of heat-killed staphylococci, streptococci, pneumococci, tubercle bacilli with some ephedrine. Several European investigators report favorable results with this product and Kammerer recommends it when autogenous material is unobtainable.

Several American investigators[178,179,180] report favorable therapeutic results using a bacterial antigen complex made by the Hoffman method. This is a process of coprecipitation that produces an acellular antigen complex, containing both the soluble and insoluble specific protective substances with the antigenic toxin.

Prigal points out the frequent intrafamiliar contagion in chronic sino-respiratory infections. When prophylactic measures, such as isolation, fail, he uses autogenous vaccines both for the patient and, if possible, for the carriers. He stresses that infections of the skin and eye in the patient or relative may act as a focus for infection and re-infection of the respiratory tract. Prigal apparently attempts to build up this immunity with vaccines regardless of whether the patient has already become sensitized.

The many different methods of applying vaccine therapy is further proof

of our inadequate knowledge in this field. Frequently we do not even know whether we are giving a specific or nonspecific form of treatment. There can be no ideal treatment until a method of preparing an unchanged antigen is found. Fortunately, with our present forms of treatment many patients are helped and some progress in research is being made.

The prophylactic therapy of tetanus infection was discussed by Joseph J. Kraut[181] at the Fourth European Congress of Allergy. Despite the fact that we have a method of active immunization against tetanus infection at our disposal, Kraut calls our attention to recent statistics published by the World Health Organization showing that presently thousands of lives are being lost yearly as a result of this dreaded infection. It is very important to give a booster injection after active immunization every four to five years, and also an additional injection at the time of a tetanus-prone injury. The aqueous toxoid induces a more rapidly increasing serum titer level than the alum-precipitated type. On the other hand, the protective serum titer of the alum-precipitated toxoid will last for a longer period of time than is the case with the aqueous toxoid. About one out of 5,000 injections will be accompanied by reactions. Most of these are mild in nature, but if the patient is extremely sensitive to the culture media he may get a systemic reaction; therefore, a history must be obtained before administering the material. When a scratch test with a drop of undiluted toxoid, or an intradermal test with 0.02 ml of toxoid, ten times diluted, results in local wheals, erythema, and induration—immediately or several hours after the test—one must proceed with caution. Very many of the patients can tolerate the toxoid when given in fractional doses at weekly or longer intervals. In such cases, I always use a toxoid with different constituents.

Although passive immunization is not as dependable as active immunization in protecting the patient, when an unimmunized person suffers a tetanus-prone injury, passive immunization is necessary. In these patients, of course, extreme caution is necessary. The administration of a heterologous serum, for example, can cause a severe or even fatal reaction if the patient's sensitivity has not been determined prior to administration. Unfortunately, there is no test which gives absolute information as to the patient's sensitivity to the serum. Kraut recommends the following precautions: (1) when a scratch test results in wheal and erythema formation within fifteen to twenty minutes, the serum is not safe for use; (2) when a conjunctival test produces redness, lacrimation, or itching of the eyes on using 1:10 or 1:100 serum dilutions, the serum is unsafe; (3) when an intradermal test with 1:10 or 1:100 serum dilutions results in wheal and erythema formation within fifteen to twenty minutes, the administration of the serum is not considered safe. In such cases, however, with an added negative ophthalmic test, the serum may usually be given in fractional doses at twenty-minute intervals.

When heterologous antitoxin is unsafe, homologous antitoxin can be given. This can be administered in the form of transfusion of actively immunized human blood, or by plasma obtained from this type of blood, or by using the gammaglobulin fraction filtered from the hyperimmunized human blood. No sensitivity test is necessary before the use of this therapy. There are no known specific counter-indications for the use of homologous serum. The only risk in this type of therapy is the possible risk of infection transmitted by giving human blood or its derivative, and the very remote risk involved in the administration of gammaglobulin itself.

The minimum required serum antitoxin level for protection is 0.1 units per ml. This is usually achieved within seventy-two hours following the

administration of 1,500 units of antitoxin subcutaneously. Since the incubation time of tetanus can be prolonged for ten to fourteen days, the antitoxin administration is of value even when given several days after the injury. Simultaneous active and passive immunization is still a controversial subject.

BCG VACCINATION

The literature, most of which is foreign, on BCG is voluminous. Toxic reactions to BCG, such as tuberculosis, measles, adenitis, bronchopneumonia, silicosis, psoriasis, choroiditis, sarcoidosis, keratoconjunctivitis, and abscess at the site of vaccination have been reported. When we consider that BCG vaccination is compulsory in many countries, and that probably over 150 million people throughout the world have been vaccinated with this material, the number of adverse reactions is very small compared to the great number of beneficial results. The laboratory and clinical studies done on BCG exceed any other work carried out on other vaccines; particularly in Russia, there is a large literature on BCG. Since its introduction into Russia, the rate of incidence among pre-school children is now five to six times, in adolescents six to seven times, and in young adults nine times less than among corresponding groups of non-vaccinated persons. It is also reported that the disease runs a more benign course in vaccinated subjects. According to Berkos,[182] the destructive types of lesions and generalized forms of tuberculosis have disappeared in children in Russia. After BCG vaccination in Denmark, about one child out of every 100,000 to 175,000 had a complication, which was usually perforating adenitis developing twelve to sixteen months after vaccination. Among four million people who received BCG vaccination in the Scandinavian countries, four fatal cases were reported.

Detmold and associates[183] recently reported the case of a two-and-one-half-year-old child who contracted miliary tuberculosis, which recurred twice in the following years. Both human and bovine strains of *M. tuberculosis* could be demonstrated in the stomach washings, urine, and cerebrospinal fluid, and the patient also, for a time, had a tuberculosis ulcer of the vagina. Tuberculin sensitivity developed only for a short period and was not marked, while bacterial allergy apparently was absent. The girl did not have agammaglobulinemia, but died upon developing tuberculous meningitis. The histologic postmortem sections were of a non-specific inflammatory character. No tubercles or caseation were found and no primary complex was demonstrable. The authors believed that the tuberculous and acute infection and death were due to BCG immunization.

At the Hopital Laennec, Paris,[184] ninety-two infants gave a delayed intradermal reaction to BCG when the test was given at the same time as, or shortly before, a BCG vaccination. The reaction to the test would appear at about the same time as the vaccination reaction, with quite similar characteristics.

One of the best-planned and best-controlled studies on the efficacy of BCG vaccinations was carried out by the Medical Research Council of Great Britain.[185] The survey covered 50,000 school children, and the results confirmed the favorable reports of other countries.

In 1957, the Medical Advisory Committee of the American Medical Association reported on the present status of BCG vaccine and pointed out the need for an effective vaccine. With the new freed dried vaccine in use, it is now possible to completely standardize viability and sterility of BCG as well as to determine its safety for distribution. The multiple

puncture method, frequently practiced in the United States, is believed to have advantages.

For a complete and excellent study on BCG vaccination, the monograph by Rosenthal[186] is recommended.

MICROBIAL ALLERGY OF THE EYE

There is a vast ophthalmologic literature on microbial allergy which is to be expected because the eye and its adnexae offer an unusual opportunity to see and study allergic reactions. Not only can eye tissues be sensitized readily by microbial products, both locally or as a part of the general sensitization, but also many destructive eye lesions, formerly thought to be infectious and toxic, are now known to be allergic. And as Theodore and Schlossman write in the preface to their excellent book "Ocular Allergy," "An increasing number of apparently unrelated ocular infections are now best explained on the basis of hypersensitivity."

In January 1960, C. Smith spoke on "pathology in relation to some ocular allergic conditions."[187] It is his opinion that, in some ocular allergic conditions, the allergic responses associated with infection are more important than the exogenous allergens. Such responses may be viral as in molluscum contagiosum, bacterial as in tuberculosis, or parasitic as in toxoplasmosis. In many instances, the primary invasion may cause much less damage than the secondary allergic reactions which occur as immunity builds up.

Braley[188] classifies ocular allergy into three basic types: (1) corneal edema with or without deep vascularization, (2) phlyctenular keratoconjunctivitis, and (3) marginal infiltration ulcers. The first two are often due to allergy of external causes, and the third is generally due to various types of bacterial and viral allergy. He emphasizes both the importance of taking a careful history and the institution of proper therapy in each case. When it was not possible to remove the offending agent, Braley has had good results with the use of staphylococcal toxoid and antitoxins as a nonspecific agent.

Theodore[189] divides eczema of the eyelids into three major forms. The first is a contact allergy caused mostly by drugs or cosmetics; while the second is a staphylococcal eczema, secondary to infections of the eyelids, Meibomian glands and conjunctiva—which is due to toxigenic staphylococci. He finds this type, which is the form most frequently encountered in the practice of the ophthalmologist, to be the most common cause of chronic eczema of the eyelids. The third type is a nonspecific eyelid reaction that may be the cardinal feature of such generalized dermatoses as dermatitis, neurodermatitis, and seborrheic dermatitis. According to Theodore's findings, staphylococcus eczema most often occurs among middle-aged women with sensitive allergic skins who have manifestations of mild hypothyroidism, as well as seborrhea, with verrucous eyelid lesions. These cases frequently go unrecognized and are unsuccessfully treated as contact allergies because the differential diagnosis cannot be made from the character of the dermatitis alone. A diagnosis can be made only by demonstrating that the focal point of the process is in the eyes and their appendages, rather than in the skin. For this, cytologic examinations and cultures, as well as routine ocular examinations, are necessary.

Donegan[189a] differentiates staphylococcal eczema from contact dermatitis by: (1) Blepharitis, with scaling and frequent small ulcers of the lid margins; (2) Meibomitis, either diffuse or focal: (3) superficial epithelial

keratitis; (4) strongly positive conjunctival and lid margin cultures; (5) absence of eosinophils in the epithelial scrapings.

In staphylococcal eczema of the eyelids, according to Theodore,[189-192] dual mechanisms seem to exist. The one is the direct toxic action of the dermonecrotizing, thermolabile, and filterable exotoxin of the staphylococcus, while the other apparently is allergy to staphylococcal products, including the exotoxins, endotoxins, and possibly the staphylococcal protein itself.

Because many people previously exposed to staphylococcus show some sensitivity, ophthalmologists have differing opinions about the value of intradermal skin tests to staphylococcus toxin or toxoid. Theodore claims that marked reactions to injections of dilute staphylococcus toxoid or vaccine are valuable. "The toxic reaction, being reciprocally dependent on the blood antitoxin titer provides an index of immunity to staphylococcus infection; the allergic reaction, which is of shorter duration, is uninfluenced by dilute toxin, heated toxin, or toxoid." He uses toxoid or vaccines in treating the more resistant cases, as this increases antibody titers and is a form of desensitization therapy. Injections should begin with very low doses and be increased cautiously. Best therapeutic results occur when there are marked initial reactions. Although allergic reactions from fungi and their products are quite common in other parts of the body, Theodore believes that these are rarely found as conditions of the eyelids. Eczematous dermatitis of the eyelids due to fungi is mostly dermatophytids or monilids, and although removing the focus of infection usually clears up the condition, sensitivity to the specific fungus product remains. Theodore also mentions that foreign observers consider fungus allergy an important cause of ocular eczema.

Many investigators believe that marginal blepharitis has an allergic background, because protein substances and toxins generated in the growth of bacteria and pathogenic molds are said to have the capacity for producing allergic reactions in the skin of the eyelids or in the conjunctiva. Such patients often have dry scales and a dermatitis of the ear and ear canals. Stauffer[193] experienced good results in these cases by using staphylococcus toxoid, dust, and mold vaccines.

Palich-Szanto and Szecsi[194] recommended desensitization therapy for ocular allergy. They have had good therapeutic results by using injections of the patient's own serum, although one patient developed scrofulous conjunctivitis and corneal inflammations. In this case, a tuberculous allergy was believed to be the cause.

REFERENCES

125. Spoujitch, V.: The complexity of allergic reactions. Acta Allergol., Suppl. VII:112, 1960.
126. Prigal, S. J.: Allergy and multiple sclerosis. J. Allergy, 27:170, 1956.
127. Prigal, S. J.: Fundamentals of Modern Allergy. New York, Toronto, London: McGraw-Hill Book Co., Inc., 1960.
128. Burky, E. L.: The production in the rabbit of hypersensitive reactions to lens, rabbit muscle and low ragweed extracts by the action of staphylococcus toxin. J. Allergy, 5:466, 1934. Cited by Prigal.
129. Swift, H. F. and Schultz, M. P.: Synergic stimulating effect of hypersensitivity to foreign protein and bacteria. J. Exper. Med., 63:725, 1936. Cited by Prigal.
130. Swift, H. F. and Schultz, M. P.: Studies in synergy: The synergic action of staphylotoxin and beef lens extract in rabbits. J. Exper. Med., 63:703, 1936. Cited by Prigal.
131. Malkani, M.: BCG vaccination and other methods of tuberculosis control. J. Indian M. A., 27:368, 1956.

132. Jensen, J.: Modern concepts in medicine. St. Louis: C. V. Mosby Co., 1953. Cited by Prigal.
133. Prigal, S. J.: The inter-relationship of allergy, infection, and the psyche: A "unified field theory" for the allergist. Rev. Allerg. & Immunol., 14:190, 1960.
134. Prigal, S. J. and Dubos, R. J.: Effect of allergic shock on fate of staphylococci in the organs of mice. Proc. Soc. Exper. Biol. & Med., 93:340, 1956.
135. Filipp, G. and Szentivanyi, A.: Anaphylaxis and the nervous system. Part III. Ann. Allergy, 16:306, 1958.
136. Hansel, F. K.: Clinical Allergy. St. Louis: C. V. Mosby Co., 1953.
137. Forman, J.: Chronic Urticaria. South. M. J., 44:11, 1951.
138. Forman, J.: Asthma due to bacteria. The atopic type. Ohio State Med. J., 31:200, 1935.
139. Herxheimer, H., McInroy, P., Sutton, K. H., Utidjian, H. L. and Utidjian, H. M. D.: Acta Allergol., 7:380, 1954.
140. Walzer, M.: Chapter 12. *In* Fundamentals of Modern Allergy. Samuel J. Prigal, ed. New York, Toronto, London: McGraw-Hill Book Co., 1960.
141. Blatt, H., Nantz, F. A. and Rehm, J. M.: An improved tissue culture technique adaptable to clinical testing for bacterial hypersensitivity of the tuberculin type. Ann. Allergy, 7:170, 1949.
142. Nantz, F. A. and Blatt, H.: The application of a tissue culture technique in the clinical evaluation of bacterial hypersensitivity. Ann. Allergy, 5:554, 1947.
143. Peshkin, M. M.: Allergy in Children. Progress in Allergy III., 21-141. New York, and Basel: S. Karger, 1952.
144. Swineford, O., Jr.: Studies in bacterial allergy III. Results of 3,860 cutaneous tests with thirty-four crude polysaccharide and nucleoprotein fractions of 14 different bacteria. J. Allergy, 20:420, 1949.
145. Behounkova, L., Malota, H. and Marsalek, E.: Mikrobielle Gesamtantigene in der Behandlung allergischer Zustaende und chronischer Entzuendungen. Allergie u. Asthma, 6:326, 1960.
146. Mulder, J.: Theses. Groningen, 1937.
147. Muller, F. and Colli, A.: Das Echo-Virus-Exanthem. Deutsche med. Wchnschr., 84:1053, 1959.
148. Bergman, Sven, Colldahl, Helge and Nilson, E.: Bronchial infection in asthma and B.S.R. with a description of a method for sterile removal of bronchial secretion. Acta allergol., 8:163, 1955.
149. Hansel, F. K.: Allergy in Relation to Otolaryngology. St. Paul, Minn.: Bruce Publishing Co., 1949.
150. Bryan, W. T. K. and Bryan, M.: Significance of mast cells in nasal secretions. Tr. Am. Acad. Ophth., 63:613, 1959.
151. Frankland, A. W.: Bacterial Vaccine Therapy, p. 58-59. *In* the Therapy of Bronchial Asthma. Proceedings of the International Round Table Friendship Meeting of Allergologists held at Utrecht, Holland, in 1955. Edited by Jhr. Dr. W. J. Quarles Van Ufford. H. E. Stenfert Kroese, N. V., Publishers, Leiden, 1956.
152. Frankland, A. W., Hughes, H. W. and Gorr, R. H.: Autogenous bacterial vaccines in the treatment of asthma. Brit. M. J., 2:941, 1955.
153. Colldahl, H.: *Discussing* Frankland: Bacterial Vaccine Therapy, p. 60. *In* The Therapy of Bronchial Asthma. Proceedings of the International Round Table Friendship Meeting of Allergologists, held at Utrecht, Holland, in 1955. Edited by Jhr. Dr. W. J. Quarles Van Ufford. H. E. Stenfert Kroese, N. V., Publishers, Leiden, 1956.
154. Hajos, J.: Brit. M. J., 2:1563, 1959. Cited by Heladder.
155. Urbach, E. and Gottlieb, P. M.: Allergy. New York: Grune & Stratton, 1946.
156. Kaemmerer, H. and Michel, H.: Allergische diathese und allergische erkrankungen. Chapter V. Munich: J. F. Bergmann, 1957.
157. Wilken-Jensen, K.: *Discussing* Frankland: Bacterial Vaccine Therapy. *In* The Therapy of Bronchial Asthma. Proceedings of the International Round Table Friendship Meeting of Allergologists, Utrecht, Holland, 1955. Edited by Jhr. Dr. W. J. Quarles Van Ufford. H. E. Stenfert Kroese, N. V., Publishers, Leiden, 1956.
158. Hodek, B.: Autogenous vaccine therapy in allergic upper respiratory diseases. Allergie u. Asthma, 5:39, 1959.
159. Helander, E.: Bacterial vaccines in the treatment of bronchial asthma. Acta Allergol., 13:47, 1959.

160. Van Ufford, W. J. Quarles: *Discussing* Frankland: Bacterial Vaccine Therapy. *In* The Therapy of Bronchial Asthma. Proceedings of the International Round Table Friendship Meeting of Allergologists held at Utrecht, Holland in 1955. Edited by Jhr. Dr. W. J. Quarles Van Ufford. H. E. Stenfert Kroese, N. V., Publishers, Leiden, 1956.
161. Newport, N. M.: The use of autogenous vaccines grown in the patient's own blood. Paper presented before the Ohio Valley Allergy Society. Columbus, Ohio, May 22, 1960.
162. Sanchez-Cuenca, B.: *Discussing* Frankland: Bacterial Vaccine Therapy. *In* The Therapy of Bronchial Asthma. Proceedings of the International Round Table Friendship Meeting of Allergologists held at Utrecht, Holland, 1955. Edited by Jhr. Dr. W. J. Quarles Van Ufford. H. E. Stenfert Kroese N. V., Publishers, Leiden, 1956.
163. Hebald, S.: Specific injection treatment of hay fever and asthma. New York J. Med., 55:3637, 1955.
164. Sherman, W. B.: Asthma. *In* Textbook of Medicine by Russell L. Cecil and Robert F. Loeb. Philadelphia: W. B. Saunders Co., 9th Edition, p. 481, 1955.
165. Henricksen, E.: Specific desensitization of patients with bronchial asthma (follow-up examination). Acta Allergol., 6:208, 1953.
166. Moretti, J.: Treatment of Bronchial Asthma, p. 285. *In* The Therapy of Bronchial Asthma. Proceedings of the International Round Table Friendship Meeting of Allergologists, held at Utrecht, Holland, in 1955. Edited by Jhr. Dr. W. J. Quarles Van Ufford. H. E. Stenfert Kroese, N. V., Publishers, Leiden, 1956.
167. Spuzic, V., Danilovic, W. and Vukobratovic, S.: A Critical Review of the Treatment of Bronchial Asthma, p. 304. *In* The Therapy of Bronchial Asthma. Proceedings of the International Round Table Friendship Meeting of Allergologists, Utrecht, Holland, 1955. Edited by Jhr. Dr. W. J. Quarles Van Ufford, H. E. Stenfert Kroese, N. V., Publishers, Leiden, 1956.
168. Blatt, H.: Concomitant administration of desensitization injections and oxytetracycline. Antibiot. Med., 1:12, 1955.
169. Blatt, H.: Determination of dosage for tetracycline and oxytetracycline when used in conjunction with injections of bacterial filtrate for desensitization. Antibiot. Med., 5:19, 1958.
170. Rose, J. M.: Bacterial hypersensitivity. Texas J. Med., 51:73, 1955.
171. Tabart, J.: Role and Treatment of Infection of the Upper Respiratory Tract. *In* The Therapy of Bronchial Asthma, p. 229. Proceedings of the International Round Table Friendship Meeting of Allergologists, Utrecht, Holland, 1955. Edited by Jhr. Dr. W. J. Quarles Van Ufford. H. E. Stenfert Kroese, N. V., Publishers, Leiden, 1956.
172. Jimenez-Diaz, Carlos and Arjona, Trigueros, E.: Le rôle de l'infection dans la genèse maladies allergiques. Acta Allergol. (suppl. 3) 6:105, 1953.
173. Heise, H. A.: The role of streptococci in bronchial asthma. Ann. Allergy. 7:240, 1949.
174. Baird, K. A.: Effect of bacterial antigen plus antibody on bronchial asthma. Ann. Allergy, 10:153, 1952.
175. Baird, K. A.: Sinusitis, allergy and bacterial vaccine. Ann. Allergy, 7:339. 1949.
176. Storck, H.: Zur Vaccinebehandlung bei mikrobiell allergischen Reaktionen. (Vaccine Treatment of Microbial Allergic Reactions). Hautarzt, 8:488. 1957.
177. Randolph, T. G. and Rollins, J. P.: Pyromen in the treatment of perennial allergic symptoms. Ann. Allergy, 8:626, 1950.
178. Spielman, A. D.: Treatment of infectious asthma and respiratory infections with an acellular bacterial antigen. New York J. Med., 55:2121, 1956.
179. Spielman, A. D.: Treatment of infectious asthma and respiratory infections with an acellular bacterial antigen complex. New York J. Med., 55:1603, 1955.
180. Shinefield, M. A.: The use of autogenous acellular bacterial antigen complex in the treatment of recurrent respiratory infections and asthma in infants and children. New York J. Med., 56:1466, 1956.
181. Kraut, J. J.: Prophylactic therapy of tetanus infection. Acta allergol., Suppl. 7:396, 1960.
182. Berkos, K. P.: Vaccination against tuberculosis in the USSR. Tuberk., 35:14, No. 7, 1957. Abstracted in "Abstracts of World Medicine," 24:23, 1958.

183. Detmold, J. G., Joppich, G. and Sinapius, D.: Uber vollige Resistenz-losigkeit bei tuberkulose im Kindesalter. Deutsche Med. Wchnschr., 85:104, 1960.
184. Bernard, E., Cros-Decam and Joublioux, L.: Le BCG test d'accompagnement. Definition, signification, applications pratiques. (The BCG test of accompaniment. Definition, significance, and practical application). Presse med., 65:1547, 1957.
185. BCG and Vole bacillus vaccines in the prevention of tuberculosis in adolescents; first (progress) report to the Medical Research Council by their Tuberculosis Vaccines Clinical Trials Committee. Brit. Med. J., 1:413, 1956.
186. Rosenthal, A.: Follow-up study of fatal penicillin reactions. J.A.M.A., 167:1118, 1958.
187. Smith, C.: Pathology in relation to some ocular allergic conditions. (Proceedings of the British Association of Allergists). Acta Allergol., 15:180, 1960.
188. Braley, A. E.: Ocular allergies. Tr. Am. Acad. Ophth., 62:826, 1958.
189. Theodore, F. H.: Differentiation and treatment of eczema of the eyelids. Tr. Am. Acad. Ophth., 58:708, 1954.
189a. Donegan, J. M.: Ocular allergies. Ann. Allergy, 13:559, 1955.
190. Theodore, F. H.: Eczema of the eyelids. Ann. Allergy, 14:483, 1956.
191. Theodore, F. H.: Ocular eczema: Its classification and treatment. J. Mt. Sinai Hosp. New York, 21:255, 1955.
192. Theodore, F. H.: Symposium: Ocular Allergy: Differential diagnosis of external diseases on an allergic basis. Tr. Am. Acad. Ophth., 59:490, 1955.
193. Stauffer, H. B.: Allergic diseases of the external eye. Tr. Am. Acad. Ophth., 60:594, 1956.
194. Palich-Szanto, O. and Szecsi, S.: Desensibilisierende Therapie bei allergischen Augenerkrankungen. Ophthalmologica, 136:243, 1958.

(To be continued)

GALILEO'S REFORMS

Galileo discovered that Jupiter was accompanied by four satellites revolving about the planet, thus adding additional members to the solar system. This discovery brought additional storms of protest from the dogmatists of his day. The accredited doctrine argued that as there were seven days in the week and seven churches in Asia, so the number of planets was necessarily seven. If the number of planets were increased, then the whole system was doomed. "Moreover," argued Francesco Sizzi, "the satellites are invisible to the naked eye and therefore can have no influence on the earth, and therefore would be useless, and therefore do not exist."—Joseph Jastrow, *The Story of Human Error,* New York, Appleton-Century Company, 1936.

Papers of Interest

Grater, W. C.: Comparative effectiveness of two antihistamines in allergic rhinitis. Arch Otolaryngol 72:63-85 (July) 1960.

By means of double-blind studies, a dose of 8 mg of parabromdylamine maleate was discovered to be equivalent to 50 mg of tripelennamine as reported respectively by 83 and 58 patients.

Crawford, L. V. and Grogan, F. T.: Clinical evaluation of methdilazine hydrochloride, a new antihistamine, using double-blind and placebo control. J Tenn State Med Assoc 53:307-310 (July) 1960.

Although approximately 10 per cent of 56 patients complained of drowsiness, good effects were noted in almost 90 per cent of the patients. In allergic coryza, 25 per cent reported effects from the placebo.

Wheatley, D.: The use of long-acting sulphonamide (sulphadimethoxine) in general practice. Practitioner 185:89-95 (July) 1960.

Useful in penicillin-sensitive patients.

Bubert, H. M.: A new potent antihistamine: dimethpyrindene. Md State Med J 9:376-377 (July) 1960.

Doses of 2 mg dimethpyrindene were compared with the effects of other agents in 73 patients. Disorders treated included vasomotor rhinitis, allergic coryza and urticaria. Response was good except for drowsiness.

Fernström, Åke I. B.: Studies on procaine allergy with reference to urticaria due to procaine penicillin treatment. Acta Dermatovener (Stockh) 40:19.

Review uses dermatitis and reactions to injected procaine penicillin.

Morris, W. E.: Photosensitivity due to tetracycline. JAMA 172:1155 (Mar 12) 1960.

Associated with photosensitivity was an increase in eosinophilia. Treatment with corticosteroid hormones and diphenhydramine is suggested.

Rokseth, R.: Agranulocytosis and sepsis associated with prednisolone. Lancet 1:680 (Mar 26) 1960.

Prednisolone suggested as cause, but sepsis more likely to result in agranulocytosis.

Friedman, E. A. *et al.*: "Delayed" cutaneous hypersensitivity to leukocytes in disseminated lupus erythematosus. New Engl J Med 262:486 (Mar 10) 1960.

Intracutaneous injection of autologous leukocytes elicited delayed reaction in sixteen of twenty subjects. Of the other four, three were under influence of high doses of corticosteroid hormones. Reaction presumed due to cellular or humoral antibody or both.

Anderson, J. P.: Prolonged steroid therapy in childhood asthma. AMA J Dis Child 100:341 (Sept) 1960.

Benefits outweigh dangers in selected patients in whom routine treatment is not enough.

Sen, K. N., and Lahiri, S. C.: The effect of cortisone on histamine spasm in guinea pig ileum and bronchus. Arch Intern Pharmacodynamie 126:31 (June 1) 1960.

Contraction of guinea pig organs listed as following induction by histamine is diminished by cortisone.

Ryan, R. E.: A new approach to the symptomatic treatment of migraine. AMA Arch Otolaryng 72:325 (Sept) 1960.

In 32 of 60 patients there was complete relief which was partial in another twelve when ergotamine tartrate was administered by aerosol inhalation in doses of 0.36 mg.

Poole, R. F.: Trimeprazine (temaril) as an antiemetic and antitussive in children. N Carolina Med J 21:226 (June) 1960.

In 78 children trimeprazine was antiemetic, antitussive and sedative.

Harris, P. *et al:* Some circulatory effects of 5-hydroxytryptamine in man. Circulation 21:1134 (June) 1960.

Continuous infusion of 5-hydroxytryptamine in small quantities into the pulmonary artery in 7 subjects resulted in an increase in heart rate. There was no effect on cardiac output.

Girsh, L. S.: Allergic rhinitis, a common cause of recurrent epistaxis in children. AMA J Dis Child 99:819 (June) 1960.

Epistaxis was noted in 55 of 100 patients afflicted with allergic coryza. Incidence in 200 nonallergic children was 9 per cent. Appreciation of the role of allergy in production of epistaxis may lead to a more rational approach to therapy.

Sherwood, H. and Epstein, J.: Use of nasal decongestant and antihistamine in nasal allergies. New York J Med 60:1793 (June 1) 1960.

When the tannates of pyrilamine, prophenpyridamine and phenylephrine are used, prolonged action is noted.

Holik, S. and J. Szathmary: Titres of hemagglutinin inhibiting antibodies in the blood serum after vaccination. Ann Immunolo Hungar 2:131, 1960.

Titres average 1/200-1/300 with a maximum at 3 to 5 weeks after vaccination.

Editorial: Respiratory infections in university students. New Engl J Med 263:256 (Aug 4) 1960.

Editorial. Required reading!

Frazier, Claude A.: Reactions to stinging insects and treatment. GP 22:96 (July) 1960.

Review and case report.

Panzani, R.: Neurological and Psychological factors of bronchial asthma. Acta Allerg 7:346, 1960 (In French).

"The asthma doctor must and dare not forget that his own quiet deliberate and reassuring manner as to his absolute conviction that almost all cases of asthma can be cured, constitute one of the most important prerequisites for success."

Yu, Paul N.: The hyperventilation syndrome. Med Sci 7:532 (Apr 25) 1960.

Symptoms are listed as "inability to breathe" with a sensation of tightness in the chest or of "smothering." The patient may complain of palpitations, atypical chest pain, tachycardia, dizziness, faintness and headache. Other symptoms may be muscular stiffness, tremor or cramps and the sensation of dryness of the mouth.

Kremer, W. F.: Current uses of iodides in therapy. Clin Pharmacol Ther 1:5 (May-June) 1960.

Reviews, lists of mechanisms of effect.

Rosenblatt, Milton B.: Bronchiectasis. Med Sci 7:744 (June 10) 1960.

A review to be read and re-read.

Morris, George E.: Nylon dermatitis. New Engl J Med 263:30 (July 7) 1960.

Six cases with positive patch tests to virgin nylon are reported; a seventh patient had a positive test to a nylon stocking but did not return for further study. Patients with suspected nylon dermatitis should be tested with virgin nylon. The dyes and finishes should also be used for testing when they can be obtained.

Cohlan, S. Q.: Erythema multiforme exudativum associated with use of sulfamethoxypyridazine. JAMA 173:799 (June 18) 1960.

Clinical experience recorded by others and the five cases reported suggest that erythema multiforme exudativum may occur as a reaction to sulfamethoxypyridazine more frequently than previously reported in other sulfonamides.

Rose, K. D.: Anaphylactic reaction to aqueous chymotrypsin injection. JAMA 173:796 (June 18) 1960.

In a 19-year-old male to whom injections of aqueous chymotrypsin had been administered, severe anaphylactic shock occurred after eight days. Treatment with epinephrine, oxygen and an intravenous soluble corticosteroid preparation resulted in prompt and complete recovery.

Chakravarty, N. and Uvnas, B.: Histamine and a lipid soluble smooth-muscle stimulating principle (SRS) in anaphylactic reaction. Acta Physiol Scand 48:302 (Apr 25) 1960.

Antigen-antibody reaction in anaphylaxis activates an enzyme system, probably with essential sulf-hydryl amino group in the mast cells. This activation results in the appearance of both histamine and SRS.

Boreus, L. O. and Chakravarty, N.: Tissue mast cells, histamine and "slow reacting substance" in anaphylactic reaction in guinea pig. Acta Physiol Scand 48:315 (Apr 25) 1960.

The loss of mast cells and the release of SRS and histamine as a result of anaphylactic reaction occurring in vitro in isolated guinea pig tissue suggests that the mast cell is a source of SRS as well as histamine.

Berlin, B. S.: Gross physical properties of emulsified influenza virus vaccines and the adjuvant response. J Immun 85:81 (July) 1960.

Equal portions of virus vaccine and a mixture of one part Arlacel A and nine parts Drakeol 6 were administered in the form of an emulsion. Optimum stability is associated with maximum effect.

Stevens, A. E.: Acute adrenal insufficiency after steroid therapy in three asthmatics with pneumonia. Lancet 2:234 (July 30) 1960.

In three asthmatic patients treated with corticosteroid hormones, pneumonia and acute insufficiency of the adrenals developed.

Siegel, C.: Evaluation of a nasal decongestor in pollinosis. Minnesota Med 43:460 (July) 1960.

Good symptomatic control of hay fever is reported in 95 per cent of 128 patients in whom a timed release tablet was used. It contains phenylpropanolamine pheniramine maleate, hydrochloride and pyrilamine maleate.

Fisher, Edwin R.: Tissue mast cells. JAMA 173:171 (May 14) 1960.

Should you have missed this beautifully written paper, go to your back issues and find it.

Schenck, R. R.: Controlled trial of methoxsalen in solar dermatitis of Chippewa Indians. JAMA 172:1134 (Mar 12) 1960.

When dermatitis actinica is present, use of drug results in exacerbation. Clothing to protect skin best prophylactics.

Jones, N.: Antihistamine treatment of hay fever with special reference to the effect upon reaction time. Practitioner 185:334 (Sept) 1960.

Of 28 patients treated with 5-benzyl-1, 2, 3, 4-tetrahydro-2-methyl-carboline in doses of 50 mg administered three times daily, control of symptoms occurred in 19 including 12 in whom other antihistaminic agents had been unsatisfactory. Reaction time was increased 6-21 per cent as measured by standard tests.

Taft, E. H., Entwisle, B. R. and Langley, R.: Trimeprazine: Its assessment as an antipruritic. Med J Aust 2:208 (Aug 6) 1960.

In 55 patients a double blind study with a cross over technique demonstrated no difference between title drug and the placebo.

Sherman, W. B. and Freedman, S.: Immune milk in the treatment of hay fever. J Allergy 31:476 (Sept-Oct) 1960.

Of 26 ragweed hay fever patients treated with one quart of colostrum daily no benefits greater than those seen in 20 control subjects who took an equal amount of commercial skimmed milk were observed.

Adler, E. and Eliakim, C.: Observations on allergic reactions to the adrenocorticotropic hormone. Int Arch Allergy 17:80, 1960.

Three cases with immediate systemic reaction.

Ross, J. and Vorlaender, K. O.: Demonstration of organ-specific antigens of the kidney by precipitation in agar-gel. Int Arch Allergy 17:86, 1960.

Rabbit anti-rat kidney immune sera showed in the Ouchterlony test at least one antigen that was found organ specific by differential absorption.

News Items

THE AMERICAN COLLEGE OF ALLERGISTS
GRADUATE INSTRUCTIONAL COURSE
EIGHTEENTH ANNUAL CONGRESS

Hotel Radisson
Minneapolis, Minnesota
April 1, 2, 3, 4, 5, 6, 1962

Committee on Local Arrangements

William S. Eisenstadt, M.D., Minneapolis *(Chairman)*

Leo W. Fink, M.D., Minneapolis
S. E. Howard, M.D., Minneapolis
Clifford P. Lake, M.D., Rochester
Irvin H. Moore, M.D., Minneapolis
Lloyd S. Nelson, M.D., Minneapolis
Elmer M. Rusten, M.D., Minneapolis
Albert V. Stoesser, M.D., Minneapolis
Edward L. Strem, M.D., St. Paul

THE AMERICAN COLLEGE OF ALLERGISTS

Committee on Allergy of the Nervous System

Frederic Speer, M.D. *(Chairman)*.....Kansas City, Kansas
Theron G. Randolph, M.D. *(Co-Chairman)*.....Chicago, Illinois
William G. Crook, M.D.....Jackson, Tennessee
George S. Frauenberger, M.D.....Evanston, Illinois
Stanley L. Goldman, M.D.....Kansas City, Missouri
Philip M. Gottlieb, M.D.....Philadelphia, Pennsylvania
Stanley H. Jaros, M.D.....Harlingen, Texas
William Kaufman, M.D.....Bridgeport, Connecticut
Milton Millman, M.D.....San Diego, California
Donald C. Nilsson, M.D.....Omaha, Nebraska
Henry D. Ogden, M.D.....New Orleans, Louisiana

Pediatric Committee

At a meeting of the Pediatric Committee of The American College of Allergists on March 16, 1961 in Dallas, Texas, the following officers were elected:

Chairman.....Howard G. Rapaport, M.D.
Secretary.....Ethel M. Davis, M.D.

Members of the committee are:

Samuel C. Bukanta, M.D.....Denver, Colorado
Norman W. Clein, M.D.....Seattle, Washington
C. Collins-Williams, M.D.....Toronto, Canada
Susan C. Dees, M.D.....Durham, North Carolina
Jerome Glaser, M.D.....Rochester, New York
Salmon R. Halpern, M.D.....Dallas, Texas
Douglas E. Johnstone, M.D.....Rochester, New York
Harold I. Lecks, M.D.....Philadelphia, Pennsylvania
Samuel J. Levin, M.D.....Detroit, Michigan
George B. Logan, M.D.....Rochester, Minnesota
Thomas R. McElhenny, M.D.....Austin, Texas
John P. McGovern, M.D.....Houston, Texas
Edward S. O'Keefe, M.D.....Lynn, Massachusetts
Sydney Pedvis, M.D.....Montreal, Canada
Sheldon C. Siegel, M.D.....Los Angeles, California
Irwin A. Solow, M.D.....Pittsburgh, Pennsylvania
Frederic Speer, M.D.....Kansas City, Kansas
Victor L. Szanton, M.D.....Ansonia, Connecticut
Victor C. Vaughn, III, M.D.....Augusta, Georgia
Howard G. Rapaport, M.D.....New York, New York
Ethel M. Davis, M.D.....Chicago, Illinois

AMERICAN COLLEGE OF ALLERGISTS
EIGHTEENTH ANNUAL CONGRESS

Hotel Radisson

Minneapolis, Minnesota

April 4, 5, 6, 1962

Fellows wishing to appear on the program should submit abstracts in quadruplicate, limited to 250 to 300 words, and accompanied by a 35 to 40 word resumé-summary to Dr. Mayer A. Green, 6112 Jenkins Arcade, Pittsburgh 22, Pa., prior to November 15, 1961.

Associate Fellows are urged to submit papers in competition for the BELA SCHICK AWARD granted through the Women's Auxiliary. Instructions are the same as above.

The CLEMENS VON PIRQUET AWARD, comprising a prize of $250 and a Certificate of Award, will be presented to the Intern, Resident or Medical Student submitting the best paper on any aspect of allergy or related fields of medicine. Submit entire manuscript in quadruplicate to Dr. Green before November 15, 1961. The winning essayist need not be present to receive the Award.

Fellows, Associate Fellows and non-members wishing to display SCIENTIFIC EXHIBITS April 3 to 5, are requested to send brief summaries and descriptions in duplicate to Dr. Green before December 15, 1961.

PLEASE SUBMIT PAPERS AS SOON AS POSSIBLE.

AMERICAN COLLEGE OF ALLERGISTS
GRADUATE INSTRUCTIONAL CONGRESS

Hotel Radisson

Minneapolis, Minnesota

April 1, 2, 3, 1962

Several SCHOLARSHIPS are being generously underwritten by the Women's Auxiliary.

Applications from physicians for these SCHOLARSHIPS should be sent to Dr. Mayer A. Green, 6112 Jenkins Arcade, Pittsburgh 22, Pa. Applications from interns and residents must be accompanied by a letter of approval from the Medical Director or comparable official from the hospital they are serving.

PROMOTION TO ACTIVE FELLOWSHIP

All applications for promotion to Active Fellowship in the American College of Allergists must be completed and returned to John D. Gillaspie, M.D., Treasurer, 2141 Fourteenth Street, Boulder, Colorado, on or before *December 31, 1961,* in order to be considered for promotion at the Annual Meeting in Minneapolis, Minnesota, April 1 to 6, 1962.

The examination for promotion will be given on Tuesday, April 3, 1962.

POSTGRADUATE COURSE IN ALLERGY AND THE ENDOCRINOLOGICAL ASPECTS OF ALLERGY

The Akron Academy of Ophthalmology and Otolaryngology announces a Postgraduate Course in Allergy and the Endocrinological Aspects of Allergy to be held on November 27 to December 1, 1961 at the Sheraton Mayflower Hotel, Akron, Ohio. Additional information may be obtained from Dr. Richard H. Stahl, 2674 North Blvd., Cuyahoga Falls, Ohio.

SOCIEDADE BRASILEIRA DE ALGERIA

Newly elected officers of the Sociedade Brasileira de Alergia for the year 1961-1962 are:

President.....Dr. F. J. da Silveira Lobo, Jr.
Vice President.....Dr. Oscar Palmeira Guimaraes
First Secretary.....Dr. Sergio Camoes
Second Secretary.....Dr. Alfeu Tavares Franca
Treasurer.....Dr. Creso Castilho Ribeiro
Secretary.....Dr. Joao Rangel de Maraes

SOUTHWEST ALLERGY FORUM

A meeting of The Southwest Allergy Forum will be held at the Claridge Hotel, Memphis, Tennessee, on Sunday, Monday, and Tuesday, April 15, 16, and 17, 1962.

All members of The American College of Allergists are invited to attend. Further information may be obtained from Dr. Bernard M. Zussman, 1023 Madison Ave., Memphis, Tennessee.

WEST COAST ALLERGY SOCIETY

The West Coast Allergy Society will hold its inaugural meeting at the Fairmont Hotel, San Francisco, Saturday, December 2, 1961.

The new society, sponsored by California, Oregon and Washington allergists is organized for the purpose of an annual meeting for members of the state organizations for the discussion of allergy problems indigenous to the west. Non-members of the three societies are welcome.

WEST VIRGINIA STATE SOCIETY OF ALLERGY

At the annual meeting of the West Virginia State Society of Allergy on August 24, 1961, at White Sulphur Springs, West Virginia, the following officers were elected for the year 1961-1962:

President.....Martin D. Reiter, M.D.
Vice President.....William L. Neal, M.D.
Secretary-Treasurer.....Merle S. Scherr, M.D.

THE PITTSBURGH ALLERGY SOCIETY

At a meeting of The Pittsburgh Allergy Society the following officers were elected for the years 1961-1963:

President.....Irwin A. Solow, M.D.
Secretary-Treasurer.....Herbert C. Mansmann, Jr., M.D.

RETIREMENT

Dr. Walter Lincoln Palmer, one of the original eight faculty members of the School of Medicine of The University of Chicago is retiring from his post. He will continue with the University in an emeritus capacity.

Dr. Palmer is the author of many scientific publications dealing with the mechanism of pain in peptic ulcer, clinical aspects of the ulcer problem, gastro-intestinal ulcer, and ulcerative colitis.

In Memoriam

M. J. GUTMANN, M.D., F.A.C.A.

M. J. Gutmann, M.D., died on June 13, 1961, in Jerusalem, Israel. Doctor Gutmann was born in Heidenheim, Germany, on March 19, 1894. He studied medicine at various German universities, including Heidelberg. During World War I, he served as a non-commissioned officer in the Medical Corps. In 1920, he received his medical degree at the University of Munich.

Doctor Gutmann's immediate postgraduate training and research were carried out at the Psychiatric Research Institute of the University of Munich. During 1927-28, Doctor Gutmann attended Storm van Leuwen's Allergy Clinic at the University of Leyden (Holland) and subsequently devoted his time to the practice and research of allergy.

Doctor Gutmann was one of the pioneer allergologists in Germany and headed its first allergy department in a hospital. After the Nazi regime came to power, Doctor Gutmann settled in Jerusalem and opened his office for the practice of allergy, the first in that part of the world. He was soon appointed allergy consultant to the Rothschild-Hadassah-University Hospital.

In his lifetime, Dr. Gutmann published more than 120 scientific monographs and papers. His early works dealt with heredity, tuberculosis and psychiatry; the great majority of the later publications cover various aspects of allergy, applied immunology and related fields.

Doctor Gutmann participated actively in the activities of the Israel Medical Association and for many years chaired its committee on nutrition. He was a member of the Israel Society of Genetics.

Doctor Gutmann was rightfully considered the dean of allergologists in Israel. When he founded the Israel Society of Allergy, he was elected its first president and held this office until his death. He was a Fellow of the founding group of the International Association of Allergology and was repeatedly sent as national delegate to its House of Delegates. In 1958, the House elected him to the executive committee of the Association.

Doctor Gutmann was an Associate Fellow of the American Academy of Allergy, a Corresponding Member of the French Allergy Society, and an Honorary Member of the Argentine Allergy Society. He participated in the Collegium Internationale Allergologicum and was a contributing editor of the *International Archives of Allergy and Applied Immunology* and the *Review of Allergy and Applied Immunology*.

Doctor Gutmann became a Fellow of The American College of Allergists in 1952.

—I. G.

Book Reviews

THE FIXED ERUPTION. By Ashton Welsh, M.D. 248 pages. Springfield, Illinois: Charles C Thomas, 1961. A monograph in the Bannerstone Division of American Lectures in Dermatology, edited by Arthur C. Curtis.

Although dermatologists are well aware of fixed drug eruptions, they remain one of the least known manifestations of drug intolerance. Therefore, a monograph dealing with this particular subject should be welcomed by the medical profession.

Apparently, this book is meant to be mainly a reference work. It presents a compilation of the numerous drugs which have caused fixed eruptions, from the modern antibiotics to the not quite so modern antipyretics and arsenicals, and the material includes a discussion of those fixed eruptions caused by substances other than drugs. The book lists also the chemical formulas of the most important drugs and their cross-reactors, as well as their synonyms and trade names, both in this country and abroad.

An index makes the volume additionally valuable and the reader will find adequate information about drugs which have caused fixed eruptions, even though he consults only individual chapters. However, such an organization makes repetition inevitable. For instance, data about immunity or histology in fixed eruptions are mentioned and repeated in several places. It is the opinion of the reviewer that a single, more elaborate chapter on clinical appearance of fixed eruptions and their immunological phenomena would be a welcome revision for a future edition. There are in addition, a few statements with which the reviewer finds it difficult to concur, among them the suggestion that the LE phenomenon caused by hydralazine might be considered a phenomenon of a fixed eruption.

However, these are minor items which do not detract from the value of the book. It should prove to be a handy reference work for all medical libraries as well as for those dermatologists and others interested in the side effects of drugs.

S.E.

LOCAL FREEZING OF THE SKIN BY CARBON DIOXIDE SNOW. By Holger Brodthagen. Acta Dermato-Venereologica, Vol. 41., Supplementum 44, Stockholm 1961.

This monograph, prepared as a post-doctoral thesis, discusses briefly the historical use of cryotherapy and the modern agents used. Present-day indications are listed. Following these items, some known data about the anatomy of the skin (mainly its thickness), the nature of the cutaneous blood vessels, and thermal properties of the skin and effects of freezing are given. The rest of the work consists of accounts of experiments designed to glean information about the responses of the skin to refrigeration by solid carbon dioxide.

In particular, factors of area refrigerated, duration of refrigeration and pressure exerted in the contact of refrigerant with the skin were investigated by precision instruments with respect to depth and lateral extent of freezing achieved. As expected, it was found that the extent of freezing in a tissue "depends on the time [duration] of freezing, the area of contact and the pressure applied. . . ." It has long been known from clinical observation, even deducible *a priori* from physical principles, that degree and extent of freezing varies directly with duration, contact pressure and area of refrigeration. Practical problems of precisely how long, how hard and how large areas should be treated in particular conditions where refrigeration is therapeutically desirable are not answered by the data presented. Effective, everyday use of cryotherapy still remains in the realm of art rather than exact science. M.L.

when anxiety intensifies asthma

for effective steroid therapy with lower steroid dosage

"When significant conscious or unconscious emotional factors are present in asthmatic patients, the concurrent administration of hydroxyzine allows an appreciable lowering of prednisolone maintenance requirements."[1]